

# Effect of Progressive Addition Lenses on Myopia Progression in Japanese Children: A Prospective, Randomized, Double-Masked, Crossover Trial

Satoshi Hasebe, Hiroshi Ohtsuki, Takafumi Nonaka, Chiaki Nakatsuka, Manabu Miyata, Ichiro Hamasaki, and Shubei Kimura

**PURPOSE.** This prospective, randomized, double-masked, crossover trial was conducted to evaluate the clinical effectiveness of progressive addition lenses (PALs) compared with single-vision lenses (SVLs) on myopia progression in Japanese children.

**METHODS.** Ninety-two children fulfilling the inclusion criteria (age: 6–12 years, spherical equivalent refractive errors:  $-1.25$  to  $-6.00$  D) were randomly allocated to either 18 months of wearing PALs (near addition:  $+1.50$  D) followed by 18 months of SVLs (group 1), or 18 months of wearing SVLs followed by 18 months of wearing PALs (group 2), and were followed up for 3 years (two-stage crossover design). The primary outcome measure was myopia progression, as determined by cycloplegic autorefraction.

**RESULTS.** Eighty-six (93%) children completed both treatment periods. A mixed-model, two-way analysis of variance (ANOVA) performed using 3-year data identified a significant treatment effect of PALs compared with SVLs ( $P = 0.0007$ ), with a mean 18-month difference of  $0.17$  D (95% CI:  $0.07$ – $0.26$  D). This analysis also indicated a significant period effect ( $P = 0.0040$ ) and a significant treatment-by-period interaction ( $P = 0.0223$ ): Group 1 showed a slower myopia progression than did group 2.

**CONCLUSIONS.** The use of PALs slowed myopia progression, although the treatment effect was small, as previously reported in ethnically diverse children in the United States. The significant treatment-by-period interaction suggests that early application of PALs would probably be more beneficial for these age and refraction ranges (isrctn.org number, 28611140). (*Invest Ophthalmol Vis Sci.* 2008;49:2781–2789) DOI:10.1167/iavs.07-0385

From the Department of Ophthalmology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Okayama, Japan.

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Corresponding author: Satoshi Hasebe, Department of Ophthalmology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan; shasebe@md.okayama-u.ac.jp.

With a goal of slowing the progression of myopia during childhood, several methods, including atropine eye drops,<sup>1,2</sup> pirenzepine ophthalmic gel,<sup>3,4</sup> and progressive addition lenses (PALs)<sup>5–10</sup> have been proposed and tested in randomized clinical trials. Of all these treatment strategies, PALs are the easiest to apply in clinics because there are few side effects.<sup>11</sup> However, the clinical importance of PAL treatment, as well as its rationale, should be further investigated.

A multicenter, randomized, controlled trial in the United States, Correction of Myopia Progression Trial (COMET), reported a significant treatment effect of PALs in slowing both myopia progression and the increase in axial length.<sup>9</sup> However, the treatment effect was clinically small: 3-year treatment effect of  $0.20$  D and  $0.11$  mm, respectively. In this trial, Gwiazda et al.<sup>12</sup> proposed a treatment rationale based on evidence from animal and clinical studies. Briefly, accommodative lag is large during near work in some children, and hyperopic defocus due to this increased lag may trigger the visual regulation mechanism of ocular growth and elongate the eye. Thus, the use of PALs to facilitate accurate focusing over a range of viewing distances from near to far could slow the progression of myopia. The scenario for myopia progression in this rationale agrees with the clinical observation that children with myopia showed a greater accommodative lag than children who are emmetropic,<sup>13</sup> and that the lag increased 1 to 2 years before the onset of myopia.<sup>14</sup> However, in another longitudinal study, Mutti et al.<sup>15</sup> reported that lag elevated only after the onset of myopia, suggesting that the increased accommodative lag previously reported in children with myopia is a consequence rather than a cause of myopia. COMET has also reported that the treatment effect differs considerably among the races, although the difference is not significant because of the small sample size of some subgroups. In fact, one randomized clinical trial using PALs in children in Hong Kong found no significant treatment effect.<sup>6</sup> Thus, it is still questionable whether the use of PALs slows myopia progression in Japanese children who ethnically differ and/or live in a different environment in terms of learning, culture, diet, and language system, for example, compared to subjects in previous studies.

The prevalence of myopia in Japan is as high as that in other Asian countries.<sup>16,17</sup> Furthermore, a recent population-based, cross-sectional study in Japanese 40 years of age or older reported that myopic macular degeneration is the leading cause of monocular blindness.<sup>18</sup> In the present study, we sought to evaluate the clinical effectiveness of PAL treatment in Japanese children by using a prospective, randomized, double-masked, crossover trial and to examine whether the treatment effect is influenced by some clinical characteristics such as accommodative lag, near heterophoria, and degree of myopia, as previously suggested.<sup>9,10,19</sup> The rationale of this trial was basically the same as that for COMET: The use of PALs can slow

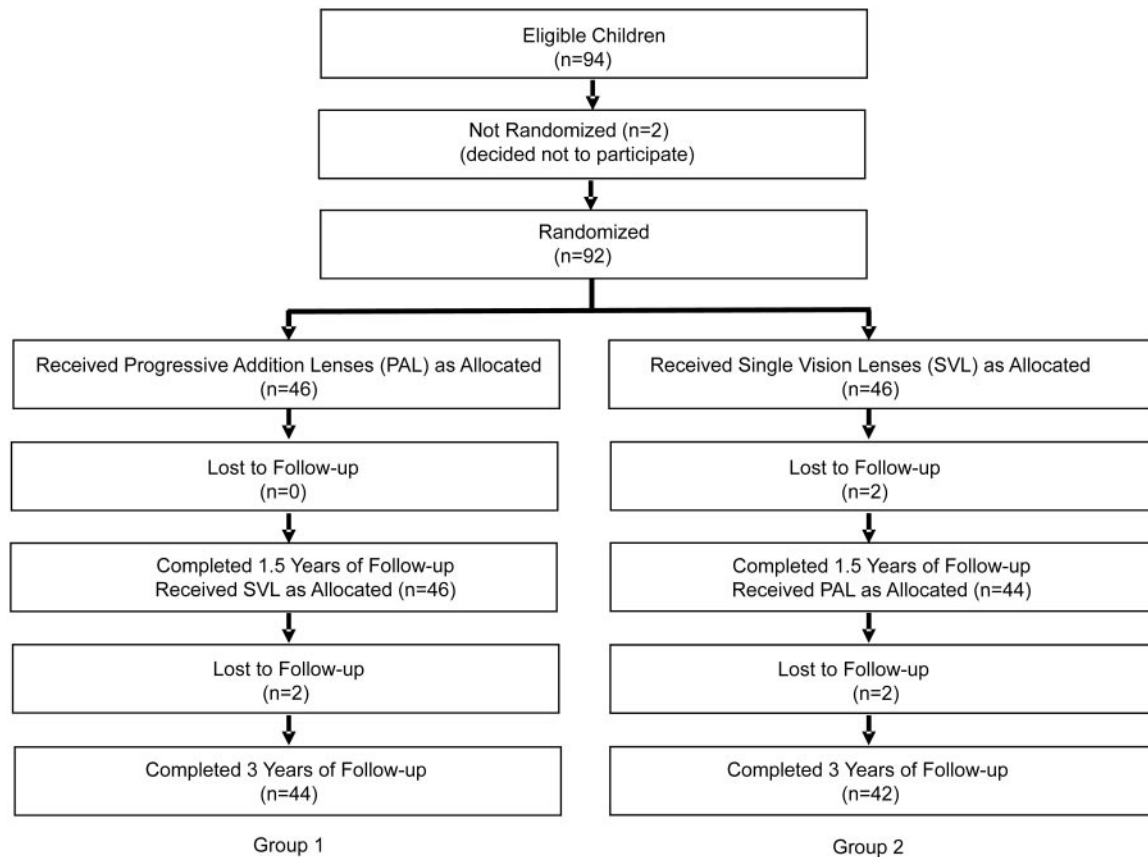


FIGURE 1. Study flow and random assignment of subjects.

the progression of myopia by reducing the lag of accommodation (hyperopic defocus) during near work.

## METHODS

### Subjects

Ninety-six children who met the criteria were enrolled between July 2002 and June 2003.<sup>20</sup> Written informed consent from parents and assent from children were obtained after written explanation and verbal discussion of the nature of the trial and possible risks and benefits. Children and parents agreed to accept the random assignment of PALs or single vision lenses (SVLs), wear the study glasses during all waking hours, and attend the follow-up visits as appointed (the children were told that “special” spectacles that may slow myopia progression would be provided in the first or second half of the follow-up period, to assess their treatment effect). The study and protocol conformed to the tenets of the Declaration of Helsinki. The ethics review board of Okayama University Medical School approved the research protocols in June 2002.

### Inclusion and Exclusion Criteria

The following inclusion criteria were applied when the subjects were recruited: (1) age from 6 to 12 years at the initial visit, (2) spherical equivalent refractive error (SER), determined by noncycloplegic autorefraction, from  $-1.25$  to  $-6.00$  D in both eyes, (3) astigmatism equal to or less than 1.50 D in both eyes, (4) anisometropia equal to or less than 1.50 D, (5) best corrected visual acuity (at 5 m) equal to or better than 1.0 (corresponds to 20/20) in each eye, (6) no manifest strabismus, (7) birth weight equal to or more than 1250 g, (8) no eye disease except for refractive error, (9) no experience of wearing PALs or contact lenses, and (10) wearing spectacles in daily life before

enrollment in the trial. Exclusion criteria included the occurrence of heterotropia or severe ophthalmic diseases that may affect refractive development.

### Study Timetable

The study design was a two-stage crossover trial. As shown in Figure 1, children were randomly allocated to wearing PALs (group 1) or SVLs (group 2) at the initial visit and were followed up every 6 months for a period of 18 months (the first period). At the 18-month visit (crossover point), children in group 1 switched spectacles from PALs to SVLs, and those in group 2 switched spectacles from SVLs to PALs. They were followed up every 6 months for another period of 18 months (the second period). The follow-up visits were scheduled so that they occurred within  $\pm 28$  days of the date specified in the protocol.

The crossover design has been widely used in clinical trials including myopia control studies.<sup>21,22</sup> This method, in which subjects serve as their own control, statistically removes between-subject variability in the background—genetic and environmental factors in the case of myopia control trials<sup>23–25</sup>—and therefore provides a greater statistical power (or requires a smaller sample size) compared with a parallel-group design.<sup>26</sup> Another advantage of using the crossover design was that all participants had an opportunity to wear PALs.

### Intervention

Children in the PAL-wearing period were provided with the lenses (MCLens; Sola International Inc., San Diego, CA), which were the same as used in the trial by Edwards et al.<sup>6</sup> This lens has a near-addition power of +1.50 D (the only addition offered) and a short corridor (10 mm) that encourages children to use the near-addition part.

The distance prescriptions for PALs and SVLs were similarly determined with the following procedure: a cylindrical lens fully correcting astigmatism determined by noncycloplegic autorefraction was set in a spectacle-testing frame, and, in addition to this lens, the lowest negative spherical lens required to attain a distance visual acuity of 1.0 was chosen. This protocol usually led to slight myopia undercorrection because the best corrected visual acuity of the participants was equal or better than 1.0. We adopted this protocol according to the results of an earlier study in Japanese children in which myopia progression was smaller with undercorrecting glasses than with fully correcting ones.<sup>27</sup> At the regularly scheduled visits held every 6 months, as well as nonscheduled visits when children reported some problems with the study glasses, objective and subjective noncycloplegic refraction was performed. When distance visual acuity corrected with the spectacles that the children were using was less than 0.7 (approximately corresponding to 20/30) in at least one eye, new lenses were prescribed according to the same protocol. These spectacles were provided to the children free of charge.

### Frame-Fitting Protocol

The spectacle frames were fitted so that the fitting point of the lenses would be just on the center of the entrance pupil with a vertex distance of 12 mm and a pantoscopic angle of 12° (conventional method used for patients who are presbyopic) at the initial visit. All spectacle frames were made of shape-memory alloys, and their nose pads were composed of silicon rubber. No instructions were given to the children regarding preferable eye or head positions while using the study glasses, because such instructions would be difficult to follow for younger children, and, thus, could introduce a confounder to the analysis. The children and parents were asked to be wary of the downward deviation of spectacles and to consult our opticians for frame-fitting correction as soon as they noticed it.

However, at the 6-month visit, video-based analysis of spectacle lens alignment revealed a considerable downward deviation of PALs.<sup>28</sup> We thus modified the fitting protocol so that the fitting point would be located 3 mm above the center of the entrance pupil. The modified protocol was applied to children when a marked downward deviation (usually >3 mm) was found at the 6-month visit or when new lenses were prescribed.

### Masking

The examiners (ophthalmologists) collecting data or prescribing spectacles were masked to the lens assignment. Parents and children were encouraged to use both types of glasses in the same way and not to discuss any issues related to the types of study glasses with the masked examiners or opticians handling the glasses. A consulting ophthalmologist dealing with any visual symptoms or matters of child safety was aware of the lens assignment, and, hence, was not involved in data collection.

### Primary Outcome Measure

The primary outcome measure in this study was 18-month myopia progression, evaluated by cycloplegic autorefraction performed at 0-, 18-, and 36-month visits. The cycloplegic agent comprised a combination of eye drops of 0.5% tropicamide and 0.5% phenylephrine (Santen, Osaka, Japan), administered 5 minutes apart. Autorefraction measures were taken 30 minutes after the initial eye drop. Similar to the 1% tropicamide eye drop,<sup>29</sup> objective assessment of residual accommodation confirmed that this type of eye drop is an effective cycloplegic agent in this study population.<sup>30</sup> Five consecutive readings were taken with an autorefractor/keratometer (ARK2000; Nidek, Gamagori, Japan) that was calibrated with a model eye before each measurement, and the average of the readings was regarded as the representative refractive error. Reportedly, this autorefractor provides reliable refractive readings during cycloplegia (repeatability coefficient,  $\leq 0.19$  D).<sup>31</sup>

Refractive errors were analyzed by expressing the reading as three components: SER,  $J_0$  (dioptric power of a Jackson cross cylinder at an

axis of 0°), and  $J_{45}$  (dioptric power of a Jackson cross cylinder at an axis of 45°), as determined by the dioptric power matrix.<sup>32</sup> The 18-month myopia progression in the first period was defined as follows: (SER at the initial visit – SER at the 18-month visit)  $\times$  548/individual duration in days between the two visits. Similarly, progression in the second period was defined as follows: (SER at the 18-month visit – SER at the 36-month visit)  $\times$  548/individual duration in days between the two visits.

### Secondary Outcome Measures

Keratometry was performed with the same equipment (ARK2000; Nidek). An average of five consecutive readings of the spherical equivalent was regarded as the representative power of the cornea (refractive index of the cornea, 1.3375).

The axial length of the eye was measured by partial coherence interferometry (IOLMaster; Carl Zeiss Meditec, Inc., Oberkochen, Germany). The device used facilitates noncontact measurement of the axial length without anesthetic eye drops and provides a higher level of repeatability regarding measurements in children ( $\pm 0.04$  mm) compared with A-scan ultrasound biometry.<sup>33</sup> This device was introduced to our clinic after the baseline measurement, and so axial length data were limited to the second period.

### Accommodative Lag and Heterophoria

Lags of accommodation were evaluated with an open-field autorefractor (WV-500; Grand Seiko, Fukuyama, Japan). Details of the measurement procedure have been published.<sup>34</sup> In short, the accommodative response of the right eye was measured while subjects were binocularly looking at a high-contrast Maltese cross located 21.0 or 32.5 cm in front of the eyes through distance-corrective lenses, determined by noncycloplegic autorefraction (roughly corresponding to an accommodative demand of 4.7 or 3.1 D, respectively). These target distances were chosen because children usually experience this level of accommodative demand during near work, and because the amount of systematic measurement error accompanying autorefraction through spectacle lenses was reported to be small ( $< 0.2$  D).<sup>35</sup> A lag of accommodation was obtained by calculating the difference between the measured accommodative response (mean of five consecutive readings) and the effective accommodative demand, which takes the vertex distance of the corrective lenses into account. The average responses to the 21.0- or 32.5-cm targets were regarded as representative of the accommodative lag.

Heterophoric angles at 33 and 500 cm were measured through the distance-corrective lenses by using the prism and alternating cover test. When an ocular misalignment was found, the cover and uncover tests were successively performed to determine whether it was heterophoria.

### Statistical Analyses

Similar to the assumption in COMET,<sup>7</sup> we anticipated a mean 18-month increase in myopia of 0.75 D in the SVL-wearing period. We wanted to have the statistical power to detect a 33% reduction in myopia progression in the PAL-wearing period (18-month increase of 0.50 D); the difference would be 0.25 D. For an overall SD of 0.55 D in the cumulative 18-month follow-up measurements of refractive error change, 78 subjects are needed for a two-tailed 5%  $\alpha$  level and 80% power.<sup>26</sup> With consideration of a lost-to-follow-up percentage of 15%, we recruited 92 subjects who met the inclusion criteria.

The commercial software (JMP ver. 5.01a; SAS Institute, Inc., Cary, NC) was used for statistical analysis. Baseline characteristics were compared between the groups using the two-tailed unpaired *t*-test if normality assumptions were preserved, or Wilcoxon's sum rank test for continuous data, and the  $\chi^2$  test for categorical data. The primary analysis of myopia progression was child-based (i.e., using the mean of the two eyes). For the  $J_{45}$  values, the right eye data were used because oblique astigmatism is frequently symmetric in the two eyes. A mixed-model, two-way analysis of variance (ANOVA), with one within-subject

TABLE 1. Baseline Characteristics of the Subjects by Study Group

Variable	Group 1 (n = 46)	Group 2 (n = 46)	Difference	P
Mean age (y)	10.0	9.7	0.3	0.36
Mean cycloplegic autorefraction (D) spherical equivalent	-3.17	-3.31	0.14	0.54
Mean corneal refractive power (D)	43.41	43.61	-0.20	0.53
Mean lag of accommodation (D)	1.95	1.68	0.27	0.08
Median heterophoria at 500 cm (PD)*	-2.1	-1.8	-0.3	0.26
Median heterophoria at 33 cm (PD)*	-4.5	-4.9	0.4	0.81
Female, n (%)	21 (46)	24 (52)	-3 (-6)	0.53

PD, prism diopters.

\* Minus sign indicates exophoria.

factor (PALs or SVLs), one between-subject factor (group 1 or 2), and their interaction, was used to determine the overall 18-month treatment effect and level of significance. Subgroup analyses of the treatment effect were also conducted to examine the influence of baseline clinical characteristics such as accommodative lag, near-point heterophoria, SER, or age. The significance level was set at  $P < 0.05$ .

## RESULTS

### Trial Profile

Ninety-two children were enrolled in the study, with 46 randomized to group 1 and 46 to group 2. Clinical characteristics at the baseline were balanced, with no significant or clinically relevant differences between the groups (Table 1). All children adapted successfully to the study glasses. As previously reported, the questionnaire survey administered at each scheduled visit identified no adverse effects associated with using PALs except for a transient uncomfortable feeling in several children at the very beginning of the wearing period.<sup>36</sup> The retention rates at the 18- and 36-month follow-up visits were 98% and 93%, respectively (Fig. 1). Only six children, two in group 1 and four in group 2, failed to return for the final visit. The reasons for being lost to follow-up or excluded from the analysis included a problem in using cycloplegic eye drops

(two children), moving to another prefecture (two children), desire to wear contact lenses (one child), or the occurrence of exotropia (one child). The actual mean ( $\pm$ SD) durations of the first and second periods were  $552 \pm 19$  and  $544 \pm 18$  days, respectively.

### Effect of PALs on Myopia Progression

At the initial visit, the mean ( $\pm$ SD) SER measured by cycloplegic autorefraction was  $-3.25 \pm 1.12$  D (range:  $-1.13$  to  $-6.00$  D), which was 0.74 D higher (less myopic) than that measured by noncycloplegic autorefraction. Over the 3-year follow-up period, myopia significantly progressed in both groups (Table 2, two-tailed paired *t*-test,  $P < 0.0001$ ). The mean ( $\pm$ SE) myopia progression in the first period was  $0.89 \pm 0.06$  D and  $1.20 \pm 0.08$  D in groups 1 and 2, respectively. That in the second period was  $0.94 \pm 0.07$  D and  $0.92 \pm 0.07$  D in groups 1 and 2, respectively. It is noteworthy that the difference in myopia progression between PAL- and SVL-wearing children appeared primarily in the first period and was nearly lost in the second period (Fig. 2A).

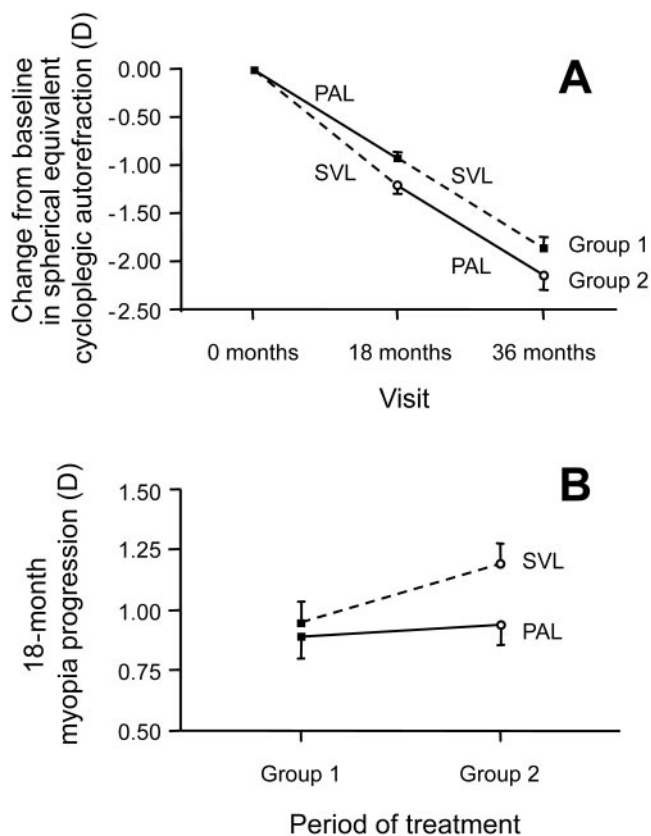
A profile plot of the data (Fig. 2B) shows an ordinal treatment-by-period interaction: Myopia progression during the PAL-wearing periods was consistently less than that in the SVL-wearing periods, but the magnitude of the treatment effect

TABLE 2. Mean Cycloplegic Autorefraction, Corneal Refractive Power, and Axial Length by Study Group at Each Stage of the Trial

Visit (mo)	Group 1	Group 2	P*	Overall
Cycloplegic autorefraction, spherical equivalent (D)				
0	$-3.17 \pm 1.08$ (46)	$-3.31 \pm 1.15$ (46)	0.54	$-3.25 \pm 1.12$ (92)
18	$-4.08 \pm 1.15$ (46)	$-4.53 \pm 1.36$ (44)	0.10	$-4.30 \pm 1.27$ (90)
36	$-4.94 \pm 1.16$ (44)	$-5.46 \pm 1.60$ (42)	0.09	$-5.19 \pm 1.41$ (86)
Cycloplegic autorefraction, J <sub>0</sub> (D)				
0	$0.07 \pm 0.25$ (46)	$0.07 \pm 0.25$ (46)	0.94	$0.07 \pm 0.25$ (92)
18	$0.17 \pm 0.38$ (46)	$0.24 \pm 0.36$ (44)	0.40	$0.20 \pm 0.37$ (90)
36	$0.29 \pm 0.43$ (44)	$0.31 \pm 0.43$ (42)	0.82	$0.30 \pm 0.43$ (86)
Cycloplegic autorefraction, J <sub>45</sub> (D)				
0	$-0.02 \pm 0.12$ (46)	$-0.06 \pm 0.14$ (46)	0.15	$-0.04 \pm 0.13$ (92)
18	$-0.06 \pm 0.19$ (46)	$-0.11 \pm 0.15$ (44)	0.14	$-0.08 \pm 0.17$ (90)
36	$-0.07 \pm 0.19$ (44)	$-0.10 \pm 0.16$ (42)	0.41	$-0.09 \pm 0.18$ (86)
Corneal refractive power (D)				
0	$43.41 \pm 1.25$ (46)	$43.61 \pm 1.47$ (46)	0.53	$43.51 \pm 1.36$ (92)
18	$43.34 \pm 1.37$ (46)	$43.57 \pm 1.28$ (44)	0.40	$43.46 \pm 1.32$ (90)
36	$43.29 \pm 1.21$ (44)	$43.55 \pm 1.46$ (42)	0.38	$43.42 \pm 1.34$ (86)
Axial length (mm)				
0	N/A	N/A		N/A
18	$25.33 \pm 0.77$ (46)	$25.25 \pm 0.81$ (43)	0.49	$25.29 \pm 0.79$ (89)
36	$25.77 \pm 0.84$ (44)	$25.64 \pm 0.82$ (42)	0.48	$25.70 \pm 0.83$ (86)

Data are the mean  $\pm$  SD (*n*). NA, not available.

\* Mean comparisons between groups 1 and 2 (unpaired *t*-test). The difference in the overall mean between the 0- and 18-month visits was significant for the spherical equivalent, J<sub>0</sub>, and J<sub>45</sub> (unpaired *t*-test,  $P < 0.01$ ). That between the 18- and 36-month visits was significant for the spherical equivalent, J<sub>0</sub>, and axial length.



**FIGURE 2.** Mean ( $\pm$ SE) change in spherical equivalent cycloplegic autorefracton (A) and profile plot showing treatment-by-period interaction (B). Two-way ANOVA indicated a significant treatment effect of PALs compared with SVLs ( $P = 0.0007$ ), with a mean 18-month difference of 0.17 D. The period effect (group 1 or 2) and the treatment-by-period interaction were significant ( $P = 0.0040$  and  $P = 0.0223$ , respectively).

(a difference between myopia progression during the PAL-wearing period and that in the SVL-wearing period) was influenced by the period (sequence) of treatment (group 1 or 2). An interesting point is that myopia progression during the SVL-wearing period was clearly less in group 1 than in group 2, whereas that during the PAL-wearing period was almost constant between the groups. Consequently, at the end of this study, mean myopia progression in group 1 was 0.29 D less than that in group 2. Two-way ANOVA (mixed model) performed using 3-year data identified a significant treatment effect of PALs compared with SVLs (sum of squares = 0.53,  $F$  ratio = 12.26,  $P = 0.0007$ ), with a mean 18-month difference in SER of  $0.17 \pm 0.05$  D (95% CI: 0.07–0.26 D). This analysis also indicated that the period effect was significant (sum of squares = 0.38,  $F$  ratio = 8.77,  $P = 0.0040$ ). The myopia progression in group 1 was less than that in group 2 with an 18-month difference of  $0.14 \pm 0.05$  D (95% CI: 0.05–0.24 D), and the treatment-by-period interaction was significant (sum of squares = 0.23,  $F$  ratio = 5.42,  $P = 0.0223$ ).

### Effect of PALs on Refractive Parameters

As mentioned earlier, axial length data were not available in the first period. In the second period, the axial length constantly increased with time (Fig. 3A, two-way ANOVA,  $P < 0.0001$ ). The 18-month axial elongation (mean  $\pm$  SE) was  $0.43 \pm 0.03$  mm and  $0.42 \pm 0.03$  mm in group 1 (SVL-wearing children) and group 2 (PAL-wearing children), respectively, with no significant difference between the two groups. The axial elon-

gation and myopia progression noted in the second period correlated strongly (Fig. 3B, Pearson's correlation coefficient =  $-0.84$ ;  $P < 0.0001$ ).

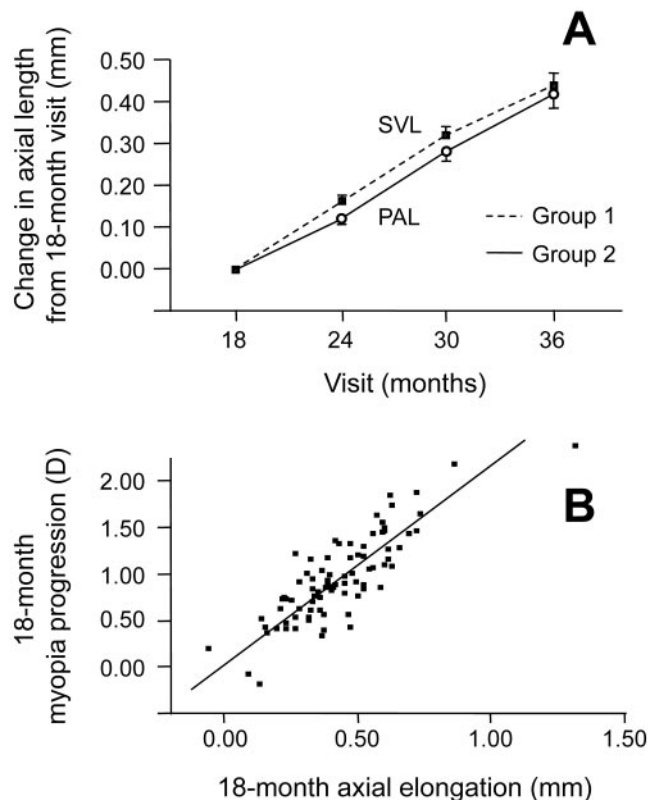
The corneal refractive power slightly decreased in the 36-month follow-up period, as shown in Table 2 (mean  $\pm$  SE:  $-0.09 \pm 0.02$  D,  $P < 0.0001$ ). There was no significant difference in the 18-month change of corneal refractive power between the PAL- and SVL-wearing periods (mixed-model, two-way ANOVA).

### Influence of Baseline Characteristics on Treatment Effect

The influence of baseline clinical characteristics on the treatment effect was analyzed separately in the first and second periods (Table 3). In the first period, a significant treatment effect was found in each subgroup, except for one group showing a smaller lag of accommodation ( $< 1.8$  D) or being more exophoric at 33 cm ( $< -4$  prism diopters). In the second period, neither of the subgroups showed a significant treatment effect regarding any of the clinical characteristics.

### Adherence and Masking

Our questionnaire survey<sup>36</sup> also indicated that the rate of adherence was slightly lower in children with low-grade myopia: wearing study glasses at all waking times was estimated to have occurred in 75% and 90% of children with  $-2$  and  $-4$ -D myopia, respectively. At the final visit, correct answers for lens



**FIGURE 3.** Comparison of change in mean ( $\pm$ SE) axial length between group 1 (children wearing SVLs) and group 2 (children wearing PALs) (A), and relationship between 18-month axial elongation and 18-month myopia progression (B) in the second period. (A) The change in the axial length did not significantly differ between the two groups. (B)  $R = -0.84$ ,  $n = 85$ ,  $P < 0.0001$ . Regression line, myopia progression =  $2.16 \times$  (axial elongation).

TABLE 3. Adjusted 18-month Myopia Progression and Treatment Effect between Study Groups by Baseline Characteristics

Baseline Characteristics	Adjusted Myopia Progression (D)*		18-Month Treatment Effect (D) PAL-SVL Mean $\pm$ SE (95% CI)
	Group 1 Mean (n)	Group 2 Mean (n)	
<b>First Period</b>	<b>PAL</b>	<b>SVL</b>	
Lag of accommodation			
Smaller lag (<1.8 D)	-0.84 (22)	-0.99 (22)	0.15 $\pm$ 0.13 (-0.11, 0.40)
Larger lag ( $\geq$ 1.8 D)	-0.87 (18)	-1.48 (18)	0.61 $\pm$ 0.15 (0.30, 0.92)†
Heterophoria at 33 cm			
More exophoric (< -4 PD)	-0.94 (20)	-1.11 (16)	0.18 $\pm$ 0.14 (-0.10, 0.45)
More esophoric ( $\geq$ -4 PD)	-0.77 (20)	-1.32 (24)	0.55 $\pm$ 0.15 (0.24, 0.86)†
Myopia			
Less myopic (> -3.3 D)	-0.78 (20)	-1.14 (17)	0.36 $\pm$ 0.15 (0.06, 0.66)†
More myopic ( $\geq$ -3.3 D)	-0.90 (20)	-1.30 (23)	0.40 $\pm$ 0.15 (0.10, 0.70)†
Age			
Younger (<10 y)	-0.89 (21)	-1.36 (23)	0.46 $\pm$ 0.16 (0.14, 0.79)†
Older ( $\geq$ 10 y)	-0.78 (19)	-1.03 (17)	0.26 $\pm$ 0.12 (0.01, 0.50)†
Overall	-0.89 (40)	-1.19 (40)	0.30 $\pm$ 0.10 (0.10, 0.50)†
<b>Second Period</b>	<b>SVL</b>	<b>PAL</b>	
Lag of accommodation			
Smaller lag (<1.8 D)	-0.99 (22)	-0.81 (22)	0.17 $\pm$ 0.13 (-0.09, 0.44)
Larger lag ( $\geq$ 1.8 D)	-0.93 (18)	-1.06 (18)	-0.13 $\pm$ 0.14 (-0.42, 0.17)
Heterophoria at 33 cm			
More exophoric (< -4 PD)	-0.82 (20)	-0.95 (16)	-0.13 $\pm$ 0.12 (-0.37, 0.11)
More esophoric ( $\geq$ -4 PD)	-1.05 (20)	-0.92 (24)	0.13 $\pm$ 0.15 (-0.17, 0.43)
Myopia			
Less myopic (> -3.3 D)	-1.00 (20)	-0.86 (17)	0.14 $\pm$ 0.14 (-0.15, 0.44)
More myopic ( $\geq$ -3.3 D)	-0.89 (20)	-1.00 (23)	-0.11 $\pm$ 0.13 (-0.37, 0.14)
Age			
Younger (<10 y)	-1.07 (21)	-1.09 (23)	-0.01 $\pm$ 0.15 (-0.31, 0.28)
Older ( $\geq$ 10 y)	-0.78 (19)	-0.75 (17)	0.03 $\pm$ 0.13 (-0.24, 0.30)
Overall	-0.94 (40)	-0.93 (40)	0.01 $\pm$ 0.10 (-0.19, 0.20)

The children were divided into subgroups using median values. The total number of subjects in each group is less than in Table 1 because of some missing data for lags of accommodation. PD, prism diopters.

\* Adjusted for all other covariates in this table.

† Significant treatment effect ( $P < 0.05$ ).

allocation were given by 65% of children. This frequency was significantly higher than 50%, or by chance (Pearson's  $\chi^2$  test,  $P = 0.017$ ), suggesting incomplete masking for lens allocation. However, the rate of adherence to wearing study glasses did not significantly differ between groups 1 and 2 at any of the scheduled visits.

### Comparisons of Residual Refractive Errors after Spectacle Correction

When comparing the distance prescription of the study glasses with cycloplegic autorefraction, the mean ( $\pm$ SE) difference (undercorrection of myopia) at the initial visit was  $0.73 \pm 0.05$  and  $0.74 \pm 0.06$  D in groups 1 and 2, respectively. That at the 18-month visit (crossover point) was  $0.73 \pm 0.05$  and  $0.74 \pm 0.05$  D in groups 1 and 2, respectively. The amount of undercorrection did not significantly differ between groups 1 and 2 at either of the two visits (unpaired  $t$ -test) or between the initial and 18-month visits in either of the two groups (paired  $t$ -test). At the end of each period, the mean amount of undercorrection increased with myopia progression ( $1.40 \pm 0.07$  and  $1.55 \pm 0.09$  D, respectively, at the 18-month visit;  $1.21 \pm 0.06$  and  $1.33 \pm 0.09$  D, respectively, at the final visit), but again, did not significantly differ between groups 1 and 2 (unpaired  $t$ -test).

## DISCUSSION

### Effectiveness of PAL Treatment

The results of this study demonstrate a significant 18-month treatment effect of PALs compared with SVLs in slowing the progression of myopia in Japanese children. However, the treatment effect ( $0.17 \pm 0.05$  D for 18 months) was clinically small, suggesting that PALs should not be routinely prescribed for children with myopia. It is difficult to make quantitative comparisons between the treatment effect in the present study and that in other ones because treatment period and/or myopia progression rate in SVL-wearing children (control) differed among them. If we compared the treatment effect using the rate of reduction of myopia progression, which is defined as (myopia progression for PALs - myopia progression for SVLs)/myopia progression for SVLs, the mean reduction rate estimated by ANOVA in our study was 15% and agrees with that in the other randomized clinical trials: Edwards et al.<sup>6</sup> and COMET<sup>9</sup> reported a reduction rate of 13% and 14%, respectively.

In crossover trials, a significant treatment-by-period interaction, as found in our trial, makes estimation of the treatment effect at the end of the study somewhat ambiguous. For example, when treating this study as a parallel-group trial and confining analysis to the first period alone (another commonly used method to analyze data from a crossover trial if the

treatment-by-period interaction is significant),<sup>37</sup> the mean 18-month treatment effect of PALs increases up to 0.31 D (95% CI: 0.11–0.50 D, reduction rate: 26%, two-tailed, unpaired *t*-test:  $P = 0.0024$ ). On the other hand, COMET, or a parallel-designed study, also reported a similar time-dependent change: the treatment effect of PALs on both myopia progression and axial elongation were observed primarily in the first year of a 3-year follow-up period.<sup>9</sup> When estimated using interpolation, its reduction rate in the beginning 18 months was 22% and was comparable with that in the present study.

When compared with clinical trials in which muscarinic receptor antagonists were used, such as atropine and pirenzepine (44%–96%),<sup>1–4</sup> the reduction rate found in our study was clearly small. This difference may imply that the development of myopia is multifactorial, and that an increasing lag of accommodation plays only a partial role. Even if lags of accommodation were eliminated by PALs, the residual retinal blur, for example, derived from off-axis<sup>38,39</sup> and/or high-order<sup>40,41</sup> aberrations of the eye may continuously evoke a response from the visual regulation mechanism of ocular growth and elongate the eye. In contrast, muscarinic receptor antagonists probably had a direct and comprehensive effect on biochemical and biomechanical properties regulating axial length in the retina, choroid, and sclera.<sup>1–4</sup>

### Clinical Factors That May Affect the Treatment Effect

We also need to anticipate several factors that might limit the clinical effectiveness of PAL treatment. First, it has not been confirmed whether PALs with +1.50 D near addition used in this trial sufficiently and consistently reduces accommodative lags in the everyday visual environment, although an effect was reported under experimental conditions.<sup>42,43</sup> This issue raises a question about the optimal amount of near addition. Leung and Brown<sup>5</sup> reported a slightly larger treatment effect with +2.00 D than with +1.50 D near addition. Coincidentally, COMET, which used +2.00 D near addition, identified a significant treatment effect, but Edwards et al.,<sup>6</sup> who used +1.50 D near addition, did not. These trials used fully correcting distance prescriptions,<sup>5–10</sup> whereas our distance prescriptions determined with the above-noted protocol involved 0.74-D undercorrection on average. Although we applied the same lens (MCLens; Sola International, Inc.) as was used by Edwards et al.,<sup>6</sup> the effective near-addition power (distance prescription + near addition) was roughly identical with that in the fully correcting distance prescription with +2.00-D near addition and may be the reason that we obtained a significant treatment effect, whereas Edwards et al. did not.

Second, undercorrection of the distant prescription itself may be a factor that reduced the treatment effect. Chung et al.<sup>44</sup> reported that spectacle undercorrection did not slow, but actually accelerated myopia progression. However, we cannot estimate the influence of this factor on the treatment effect, because the mean amount of undercorrection in the PAL-wearing period did not differ from that in the SVL-wearing period.

Finally, the downward deviation of PALs is a crucial problem in this treatment. The deviation would not induce blur during near work in children, unlike in patients who are presbyopic, and thus, it is difficult to expect them to correct it by themselves. In fact, the video-based analysis performed at the 6-month visit demonstrated a mean downward deviation of 3.7 mm (range: –0.6 to 10.2 mm), indicating that the near-addition effect of PALs was not present in some children.<sup>28</sup> We thereafter modified the spectacle-fitting protocol to overcome this problem. Despite the modification, a considerable downward deviation was occasionally found on subsequent visits.

### Treatment-by-Period Interaction

Of greatest interest in crossover trials is the interaction between the within-subject treatment effect and between-subject period effects. This interaction was significant in this study, suggesting that the treatment effect of PALs changed over time. Earlier application of PALs in children (as in group 1) was more beneficial. One well-known cause of the treatment-by-period interaction is the carry-over effect.<sup>26</sup> If the treatment effect of PALs persisted after spectacles were switched from PALs to SVLs, myopia progression in group 1 in the second period would have been less than that in group 2 in the first period (both wearing SVLs), as shown in Figure 2B. The switching of spectacles from PALs to SVLs increases the hyperopic defocus, or retinal blur, during near work, which presumably resulted in modifications in biochemical and biomechanical properties in the choroid and sclera.<sup>45,46</sup> Recent animal studies have suggested that such modification is surprisingly rapid.<sup>47–49</sup> When considering the long-term follow-up period of this trial, the carry-over effect could be ignored; hence, no washout period was incorporated into this study. However, this interpretation is a hypothesis, and the carry-over effect remains a viable explanation for the treatment-by-period interaction.

Another explanation is that the treatment effect decreased as myopia progressed. Subgroup analysis using a median split of the baseline SER (–3.30 D) found no clear difference in the treatment effect between the groups (Table 3). In contrast, COMET identified a significant treatment effect only in the subgroup with lower baseline myopia (< –2.25 D), although the splitting threshold was different from ours.<sup>9,10</sup> In the present study, the most marked myopia progression was observed in group 2 in the first period (–1.20 D on average). Consequently, the mean SER in group 2 decreased to –4.53 D at the crossover point (Table 2), and thus, 98% of the children became more myopic than was the case with the COMET splitting threshold (–2.25 D). It could be assumed that, because myopia developed and the shape of the eye became more prolate when group 2 started to use PALs, the effect of PALs in reducing hyperopic defocus on the fovea was counteracted by the increased hyperopic defocus on the peripheral retina.<sup>38,39</sup>

The third explanation is a decrease in the progression of myopia with age, which would compress the difference in progression between PAL- and SVL-wearing children in the second period. In fact, when averaged for groups 1 and 2, the mean myopia progression in the second period (0.94 D) was slightly less than that in the first period (1.04 D). This interpretation is also supported by a 3-year longitudinal study in Singaporean children with a similar baseline age range, in which older children showed a lower rate of myopia progression.<sup>50</sup>

### Clinical Characteristics at Baseline and Treatment Effect

The treatment effect of PALs was significant in the subgroup with a larger lag of accommodation and that with larger esophoria at 33 cm, at least in the first period. On the other hand, it was not significant throughout the follow-up period in the subgroup with a smaller lag of accommodation or that with larger exophoria. These results seem to be consistent with previous clinical trials using bifocals<sup>19,51</sup> or PALs<sup>9,10</sup> and indirectly support the rationale for PAL treatment. Near-point exophoria generally reduces lags of accommodation under binocular conditions via the action of cross-coupling between convergence and accommodation.<sup>52–54</sup> It is likely that PALs, which reduces the lag of accommodation, was ineffective in children who basically exhibited only a slight accommodative lag.

## Change in Axial Length and Corneal Refractive Power

Unfortunately, we did not measure axial length at the baseline, so little can be said about the treatment effect on elongation of the eye.

The mean refractive power of the cornea significantly decreased in the 3-year follow-up period, supporting the conclusions of a longitudinal study by Lam et al.<sup>55</sup> The decrease may be attributable to proportional development, or diffuse expansion, of the eye. Nevertheless, the much smaller change in corneal refractive power compared with the overall refractive change ( $-0.09$  D vs.  $1.94$  D) suggests that the influence of this factor on the treatment effect can be ignored.

## Limitations of This Trial

This study has several limitations. First, the crossover design clarified that the treatment effect of PALs changed over time. However, as mentioned, the significant treatment-by-period interaction made estimation of the treatment effect at the end of the study somewhat ambiguous. Second, we cannot confirm the treatment effect on elongation of the eye because the axial length was not measured at the baseline. Finally, modification of the spectacle-fitting protocol after the baseline was necessary to assure the near-addition effect of PALs. This could lead to underestimation of the treatment effect, as well as of the treatment-by-period interaction.

## CONCLUSIONS

The results of this crossover trial showed that the treatment effect of PALs compared with SVLs on slowing myopia progression was small but significant, supporting the conclusions of a clinical trial in ethnically diverse children in the United States.<sup>7-10</sup> The significant treatment-by-period interaction suggested that the early (at lower degrees of myopia and/or at a younger age) application of PALs to children with myopia would probably be more beneficial for these age and refraction ranges.

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