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Efficacy and safety of injection with poly-L-lactic acid compared with hyaluronic acid for correction of nasolabial fold: a randomized, evaluator-blinded, comparative study

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Summary

Background. Hyaluronic acid (HA) fillers and poly-L-lactic acid (PLA) fillers are frequently used to correct facial wrinkles.

Aim. To compare the efficacy and safety of a novel injectable poly-L-lactic acid (PLA) filler and a well-studied biphasic HA filler for the treatment of moderate to severe nasolabial folds.

Methods. In this multicentre, randomized, evaluator-blinded, comparative study, subjects were randomized for injections with PLA or HA into both nasolabial folds. Efficacy was determined by calculating the change in Wrinkle Severity Rating Scale (WSRS) relative to baseline. Local safety was assessed by reported adverse events.

Results. At week 24, mean improvement in WSRS from baseline was 2.09 ± 0.68 for the PLA side and 1.54 ± 0.65 for the HA side. Both injections were well tolerated, and the adverse reactions were mild and transient in most cases.

Conclusions. PLA provides noninferior efficacy compared with HA 6 months after being used to treat moderate to severe nasolabial folds.

Introduction

Volumetric deficiencies are increasingly recognized as a major component of the ageing process, which has led to a paradigm shift in the therapeutic approach to facial rejuvenation. To correct volume loss, soft-tissue augmentation with fillers is a widely accepted treatment. Over the past decade, the use of injectable fillers has steadily increased.[1] Fillers are prepared from a range of materials, including autologous implants, collagens, hyaluronic acid (HA), and biosynthetic polymers such as calcium hydroxylapatite, poly-L-lactic acid (PLA) and polymethyl methacrylate.

PLA is a biodegradable and bioabsorbable aliphatic polyester produced by carbohydrate fermentation of corn dextrose,[2] and was first synthesized by French chemists in 1952.[3] Each PLA molecule is relatively heavy (140 kDa), 2–50 μm in size and irregularly crystalline-shaped, all of which contribute to its slow physiological absorption. The half-life of L-polylactides is estimated at 31 days, with total absorption occurring by 18 months.[4] PLA has been used for years in resorbable surgical materials, such as sutures, plates and screws, and in membranes for guided tissue regeneration in periodontal surgery.[5]

Injectable PLA is a biostimulator rather than a traditional filler, which provides immediate volumetric

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improvement.[6] It was approved by the US Food and Drug Administration (FDA) for human immunodeficiency virus (HIV)-related facial atrophy in August 2004, and has also been used extensively in an off-label capacity to correct non-HIV-related facial volume loss.[7] As a biostimulator, PLA promotes volumization through the production of collagen and vascularization of existing collagen.[8] Its mechanism of volumetric expansion is related to a foreign-body giant-cell reaction that occurs several weeks to months after injection. In addition, the collagen production that occurs as the product degrades produces the observed volume changes and aesthetic benefit.[7]

Many studies have evaluated the efficacy of injectable PLA, but no study has compared the efficacies of injectable PLA and other procedures to improve nasolabial folds. In the present multicentre, randomized, patient- and evaluator-blinded, comparative study, we evaluated the efficacy and safety of a novel PLA filler for the treatment of moderate to severe nasolabial folds, and compared its efficacy and safety with that of a commercially available and well-studied HA filler. To our knowledge, this is the first study to investigate the subjective efficacy of injectable PLA and to compare it against an existing injectable HA product.

Methods

The study was reviewed and approved by the institutional review board of Chung-Ang University Hospital and Asan Medical Center, and performed in accordance with the principles of the Declaration of Helsinki and Korean Good Clinical Practice, and with local regulatory requirements. All subjects provided written informed consent prior to study participation.

Patient selection

This randomized, patient-blinded and evaluating assessor (EA)-blinded, treating assessor (TA)-open, comparative study was conducted at two medical centres: Asan Medical Center and Chung-Ang University Medical Center, in Korea. For study inclusion, healthy male and female adult outpatients older than 20 years were required to have moderate to severe nasolabial folds [Wrinkle Severity Rating Scale (WSRS) score of 3 or 4) that were approximately symmetrical, as judged by the TAs at each centre. The subjects had to be willing to refrain from other facial cosmetic procedures during the study period. Women of childbearing age were required to have a negative urine pregnancy test, and to use reliable contraception while participating in the study. Subjects who had undergone laser or chemical skin resurfacing, botulinum toxin injections, facelift procedures, or tissue augmentation in the nasolabial folds during the previous 24 weeks were excluded.

Materials and injection technique

AestheFill® (REGEN Biotech, Inc., Seoul, Korea) is an injectable PLA product that was recently developed for various types of soft tissue augmentation. Restylane® was the first injectable HA filler to be registered in the USA, and is the most widely used and well-studied filler for treatment of nasolabial folds. Its efficacy and safety have been investigated extensively.[9–12]

Restylane® (Q-Med, Uppsala, Sweden) is a transparent gel consisting of 20 mg/mL HA dispersed in a physiological saline solution (pH 7.0). AestheFill® is packaged as a sterile, freeze-dried preparation in a clear glass vial. We diluted 100 mg of PLA powder with 0.7 mL of saline solution 10 min before injection.

At the initial treatment visit (week 0), subjects were randomized using a computer-generated code to receive injections of one of the products in both nasolabial folds. A eutectic mixture of lidocane 2.5% and prilocaine 2.5% (EMLA; AstraZeneca, Södertälje, Sweden) was applied topically 1 h before injection. With the subject in an upright position, the products were injected into the junction of the subcutaneous and deep dermal planes, using a linear-threading technique. Preparations of both products were injected using a disposable 1.0 mL syringe with a sterilized 0.5-inch 27G needle. The TAs were given instructions to fully correct the nasolabial defects, but not to overcorrect them.

Assessment

Response to the initial injections of PLA and HA was evaluated at 2 weeks, and if deemed necessary by the EAs, a repeat treatment (touch-up) was performed by the TAs. The material injected for the touch-up was identical to that used for the initial treatment.

The visual appearance of each nasolabial fold was assessed at each visit by the EAs and TAs, using the five-point WSRS at 0, 8, 16 and 24 weeks. The degree of overall improvement in the appearance of the nasolabial folds was determined at 8, 16 and 24 weeks by the TAs and the subjects, using the Global Aesthetic Improvement Scale (GAIS) (3 = very much improved, 2 = much improved, 1 = improved, 0 = no change, and −1 = worse).

Safety assessment

At each follow-up visit, the subjects were asked about adverse events (AEs), and the TAs examined the injection sites for erythema, swelling, induration, pruritus, irritation, mass, haematoma, pain and dryness. Invisible subcutaneous papules (< 5 mm) and visible or protruding nodules can develop after an injection of PLA.

Statistical analysis

The primary efficacy endpoint was the WSRS score assessed by the EAs at week 24. The one-sided 97.5% confidence interval of the mean between-treatment difference (PLA minus HA) was calculated, and noninferiority was declared if the lower limit of the interval was > -0.29. A margin of 0.29 was chosen based on published results showing a mean between-treatment difference (previous control minus HA) of approximately 0.58 in the mean improvement in WSRS at week 24.[13]

The secondary efficacy endpoints were (i) EA- and TA-assessed WSRS scores at weeks 8, 16 and 24; (ii) TA- and patient-assessed GAIS at weeks 8, 16 and 24; and (iii) proportion of subjects with an improvement of ≥ 1 grade in the EA- and TA-assessed WSRS scores from retreatment to week 24. Mixed model for repeated measures] was used to analyze secondary endpoints (i) and (ii), while McNemar test and an odds ratio were used to analyze secondary endpoint (iii). The statistical tests for secondary efficacy endpoints were two-sided, and $P < 5\%$ was considered statistically significant.

Finally, we analyzed the correlation between efficacy and age by the Pearson correlation coefficient method. Both the PLA and HA groups were divided into four subgroups according to treatment method and mean age to compare the effects of each subgroup using paired *t*-test.

Results

Demographics

In total, 58 subjects completed the follow-up at 24 weeks; 30 subjects (3 men, 27 women) in the PLA group and 28 subjects (4 men, 24 women) in the HA group. The age (mean ± SD) was 51.9 ± 6.9 years (range 37–64) in PLA group and 52.6 ± 6.7 years (38–66) in the HA group. The subgroups were divided according to age as above or below 52 years of age. In the PLA group, 14 subjects were aged < 52 years and 16 subjects were aged > 52 years, while in the HA group, these numbers were 13 and 15, respectively (Table 1).

Table 1 Characteristics of patients.

	Groups	
	PLA (Aesthefill®)	HA (Restylane®)
Patients, *n*	30	28
Sex, *n* (%)		
Male	3 (10)	4 (14)
Female	27 (90)	24 (86)
Age, years		
Mean ± SD (range)	51.9 ± 6.9 (37–64)	52.6 ± 6.7 (38–66)
Subgroups		
≤ 52 years	14 (47)	13 (46)
> 52 years	16 (53)	15 (54)

HA, hyaluronic acid; PLA, poly-L-lactic acid.

Skin assessment

At week 24, the mean WSRS score, as determined by the EAs, was 1.37 ± 0.56 and 2.00 ± 0.79 for the PLA and HA groups, respectively (Fig. 1a). The lower limit of the one-sided 97.5% CI was 0.34, which was well above the pre-defined margin for noninferiority (−0.58), indicating that the efficacy of PLA at week 24 was comparable with that of HA.

Before the first treatment, the mean WSRS score, as determined by the EAs, was 3.47 ± 0.51 (Fig. 1a). These WSRS scores had improved at the follow-up visits at 8, 16 and 24 weeks by at least one grade in both groups, but the PLA group was slightly superior to HA group at all three follow-up points. Statistically significant differences were observed at weeks 8, 16 and 24 ($P < 0.05$). In terms of the TA-assessed WSRS score, the PLA group was also slightly superior to the HA group at weeks 16 and 24, but there were no significant differences at any time-point (Fig. 1b).

In terms of the GAIS assessed by the subjects, PLA was considered more efficacious than HA at every follow-up visit (Fig. 2a). In terms of the GAIS assessed by the TAs, PLA was significantly better than HA at every follow-up visit (Fig. 2b). There was no statistically significant difference between the two GAIS assessments at any visit.

At week 24, PLA was associated with a higher proportion of subjects with an improvement of ≥ 1 grade in the EA-assessed WSRS scores relative to the pretreatment value (100% for PLA vs. 85.7% for HA). This was also true for the TA-assessed WSRS scores (93.3% vs. 75.0%). However, neither of these differences was statistically significant. Serial photographic

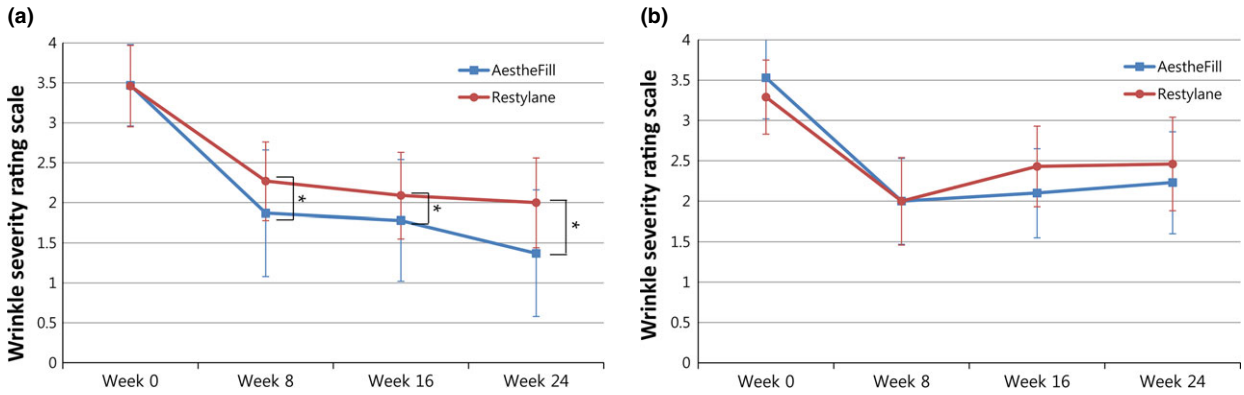

Figure 1 Wrinkle Severity Rating Scale (WSRS) scores over a 24-week period after the initial treatment (week 0) with poly-L-lactic (PLA; Aesthefill) and hyaluronic acid (HA; Restylane). (a,b) WSRS scores assessed by (a) the evaluating assessors and (b) the treating assessors. *$P < 0.05$.

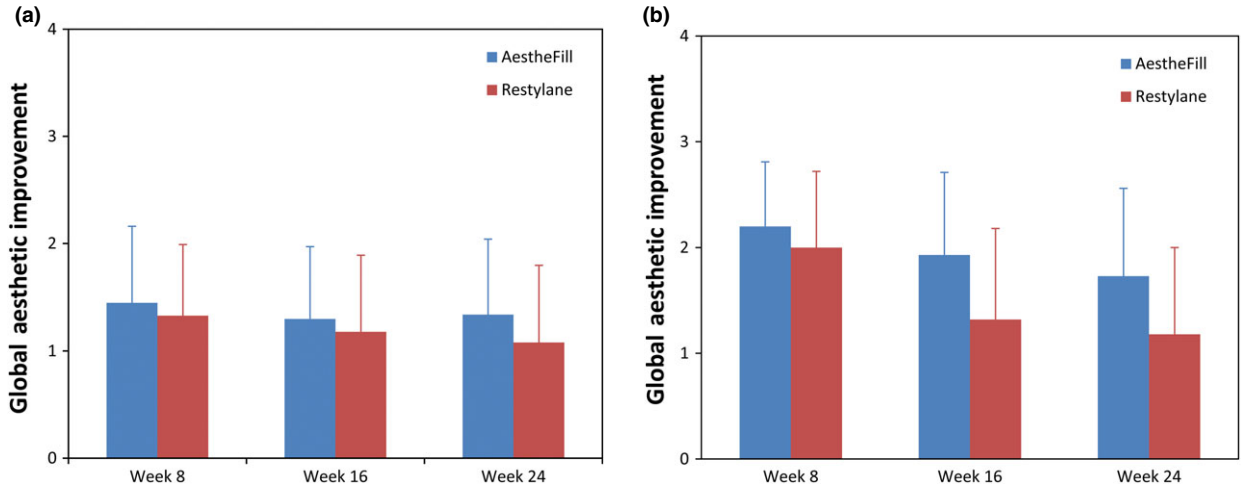

Figure 2 Global Aesthetic Improvement Scale (GAIS) scores at 8, 16 and 24 weeks. The poly-L-lactic (PLA; Aesthefill) side was associated with higher GAIS scores at all follow-up visits, but there was no statistically significant difference between the PLA and hyaluronic acid (HA; Restylane) sides. (a,b) GAIS scores assessed by (a) patients and (b) treating assessors.

images of the nasolabial folds before and after treatment with PLA and HA are presented in Fig. 3.

Pearson correlation coefficient did not reveal any statistically significant results. In the comparison of improved WSRS scores from baseline (week 0) between subgroups, there were statistical differences between patients younger and older than 52 years (Table 2). In the subgroup aged > 52 years, the HA-treated group was significantly more improved than the PLA-treated group at weeks 8, 16 and 24 for the EA-assessed WSRS, and at week 16 and 24 for the TA-assessed WSRS (Fig. 4), indicating that HA may be a better choice for older patients.

Adverse events

There were three patients with AEs related to local injection site responses, who had discoloration, nodules and vesicles, respectively, but there was no erythema, irritation, haematoma, induration, swelling, warmth, dryness or pain at the injection site in any of the patients. AEs occurred only in the PLA group and resolved without sequelae. The self-limiting nature and the short duration of the local reactions suggest that they were generally caused during the procedure rather than being product-related events or hypersensitivity responses.

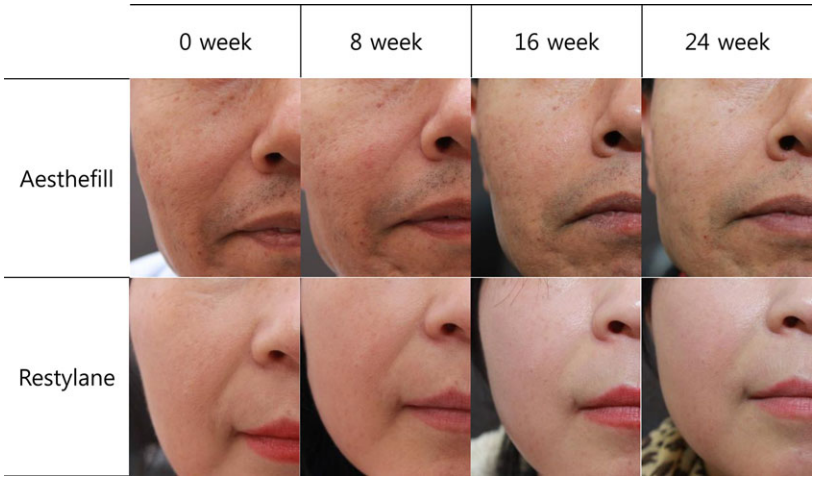

Figure 3 Photographic images of nasolabial folds of representative patients over time. Aesthefill is poly-L-lactic (PLA) and Restylane is hyaluronic acid.

Table 2 Comparison of improved Wrinkle Severity Rating Scale scores from week 0 in of each subgroup.

	Evaluating assessor			Testing assessor		
Compared group	8 weeks	16 weeks	24 weeks	8 weeks	16 weeks	24 weeks
PLA ≤ 52 vs. PLA > 52	0.984	0.085	0.249	0.164	0.565	0.408
HA ≤ 52 vs. HA > 52	0.836	0.762	0.968	0.621	0.309	0.255
PLA ≤ 52 vs. HA ≤ 52	0.182	0.344	0.628	0.947	0.534	0.933
PLA > 52 vs. HA > 52	0.008*	0.004*	0.004*	0.090	0.013*	0.044*

≤ 52, Age under 52 years; > 52, age over 52 years; PLA, poly-L-lactic acid (Aesthefill®) treated group; HA, hyaluronic acid (Restylane®). *$P < 0.05$.

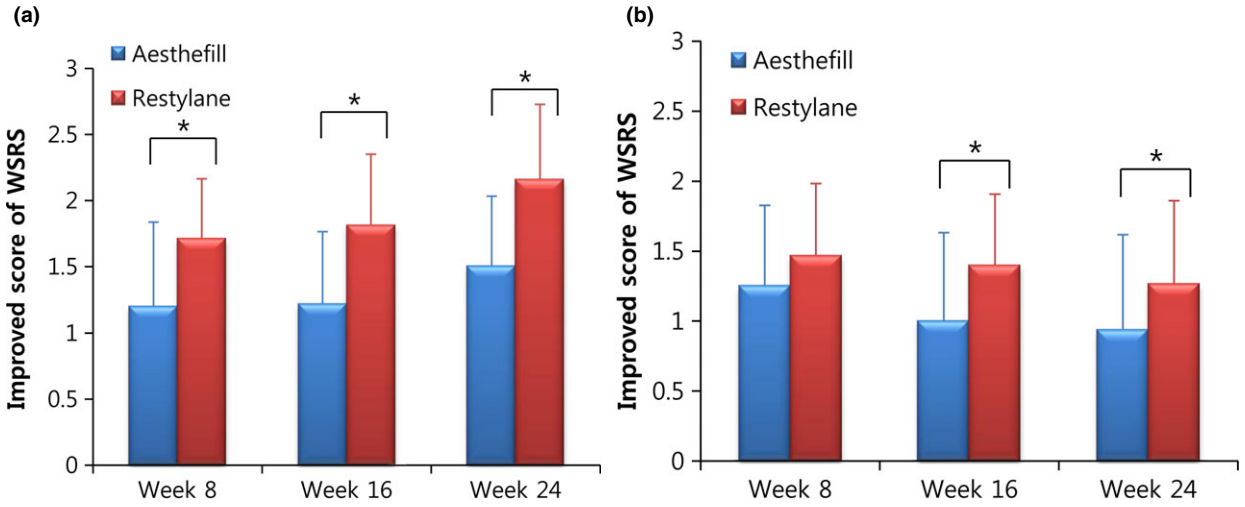

Figure 4 Improvement in Wrinkle Severity Rating Scale (WSRS) scores over a 24-week period from the initial treatment (week 0) with poly-L-lactic acid (PLA; Aesthefill) and hyaluronic acid (HA; Restylane) in subgroups aged > 52 years. (a,b) WSRS scores assessed by (a) the evaluating assessors and (b) the treating assessors. *$P < 0.05$.

No serious AEs or infections were reported, and no subjects discontinued treatment because of an AE.

Discussion

The precise mechanism of action that produces the plumping effects of injected PLA has not been fully elucidated, but it appears to be related to both host response and gradual degradation of the material.[5] Biological responses to PLA implants are histologically characterized by a classic foreign-body granuloma.[2] At 3 months after subcutaneous injection, PLA microspheres are surrounded by macrophages, lymphocytes and giant cells in a fibrous tissue capsule, consisting mostly of collagen.[14] At 6 months, the microparticles become porous and deformed, and at 9 months, there is no evidence of residual polymers or surrounding fibrosis.[4,14] Thus, although increased numbers of fibroblasts and collagen fibres are deposited as the polymers degrade,[8] the bulking effect of injected PLA appears to depend primarily on the host response.[15,16] Collagen production usually starts within 6–8 weeks after injection,[17] with type 1 collagen continuing to form for up to 9–12 months after the final treatment.[8] The 'intended' foreign-body inflammatory response, dermal fibroplasia and slow PLA microsphere degradation each contribute in varying degrees to the long-term clinical effects, which may be evident for up to 2 years.[2,5,15,18,19] This relative longevity contrasts with other temporary fillers, such as bovine/human collagen and HA.

PLA particles start to be reabsorbed around 6 months after injection and have disappeared by 9 months.[20] Polylactides are metabolized along a similar metabolic pathway to that of lactate/pyruvate.[21] Subcutaneous metabolism of PLA does not affect plasma lactate.[22,23] Tissue-implanted PLA is considered bioresorbable because it disappears as a result of enzymatic and nonenzymatic hydrolysis, which includes extracellular hydrolysis, ester cleavage and the catalytic effects of the lactic acid monomers.[3] Macrophages phagocytize the lactic acid derivatives, and lactic acid enters the tricarboxylic acid cycle, then it is metabolized and subsequently eliminated from the body as carbon dioxide and water.[8] In a study conducted using ^{14}C-labelled PLA implants, it was concluded that lactic acid is eliminated through respiration as carbon dioxide.[21]

The only specific AE of PLA injection was nodule formation. Small, palpable, inconspicuous, subcutaneous nodules, as well as visible nodules, can result from uneven distribution, superficial placement or improper reconstitution of the product.[24] In our study, only one subject reported an invisible mass-like lesion at the PLA injection site, and this resolved spontaneously within 1 month. Because the occurrence rate of visible or invisible nodules induced by PLA injection was very low, and either resolved spontaneously or were treated by subcision, nodules are not likely to be major factors in treatment selection.

PLA was found to be as effective as HA in treating moderate to severe nasolabial folds, as the efficacies of both products, as measured by mean WSRS score, were comparable for all follow-up visits. PLA was superior in terms of the proportion of subjects whose WSRS scores had improved by at least one grade at week 24, and was found to be consistently comparable to HA in terms of the GAIS assessed by the subjects at every study visit. However, our data showed interesting results in older subjects (> 52 years of age). When efficacy was compared in the total number of subjects, the results in the PLA group were better than in the HA group. However, when compared only between the subgroups of patients aged >52 years, the HA group had superior results. One possible reason is that there is a different mechanism behind the improvement of nasolabial folds between injectable PLA and HA. As mentioned above, PLA causes tissue augmentation by inducing a foreign-body inflammatory response and dermal fibroplasia. The immune response and collagen production are weaker in older than in younger adults because of the ageing process. For this reason, the soft tissue augmentation induced by PLA was lower in the older than in the younger patients, and this was similar in the HA subgroups.

Conclusion

The present comparative study showed that PLA is noninferior to HA in correcting moderate to severe nasolabial folds, and appears to have superior efficacy to HA in younger patients, in contrast to the results shown in older patients. Therefore, PLA may be a good choice for correcting nasolabial folds in younger patients. This study is the first study to investigate the subjective efficacy of PLA compared with HA filler.

What's already known about this topic?

- HA and injectable PLA fillers provide immediate volumetric improvement, and are frequently used for the correction of facial soft-tissue defects.

What does this study add?

• Injectable PLA can produce a result comparable with HLA fillers for the correction of nasolabial folds, and can be a good choice for such a treatment.

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