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A Randomized, Participant- and Evaluator-Blinded, Matched-Pair, Prospective Study Comparing the Safety and Efficacy Between Polycaprolactone and Polynucleotide Fillers in the Correction of Crow's Feet

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ABSTRACT

Background: Dermal fillers have gained widespread popularity for facial cosmetic enhancement and anti-aging treatments. Recently, polycaprolactone (PCL) and polynucleotides (PN) fillers have emerged as promising options owing to their safety and long-lasting effects.

Objectives: This study aimed to compare the efficacy and safety of a novel PCL-based dermal filler (DLMR01) with purified PN filler (RJR: Rejuran) in correcting crow's feet wrinkles.

Materials and Methods: A randomized, evaluator-blinded, prospective split-face study was conducted with 218 healthy Asian participants. The primary outcome was in the improvement rate of the Crow's Feet Grading Scale (CFGS) at rest after 12 weeks. Secondary outcomes included the improvement rate of the CFGS at expression and rest at earlier time points, changes in CFGS, and the Global Aesthetic Improvement Scale (GAIS) assessment.

Results: The results showed that DLMR01 was not inferior to RJR in improving crow's feet wrinkles, with a significantly higher CGFS improvement rate at week 12. Both fillers demonstrated good safety profiles, with mild and tolerable adverse events. No serious adverse events were reported during the study period.

Conclusion: DLMR01, a PCL-based dermal filler, showed effectiveness and safety in improving wrinkles described as crow's feet. The study suggests that DLMR01 could be a promising option for noninvasive anti-aging treatments.

1 | Introduction

Dermal fillers have been widely used since the 1980s in the cosmetic enhancement of the face area for those who want to slow the aging process, while dermal filler injections have become increasingly popular in anti-aging processes [1]. Depending on effectiveness and durability, there are several types of dermal fillers, which include nonanimal stabilized hyaluronic acid (NASHA), calcium hydroxylapatite (CaHA), and poly-L-lactic acid (PLLA). Recently, in the beauty market, there has become

[Correction added on 28 January 2025, after first online publication: The text "pegylated PCL" was changed to "PCL" throughout the entire document. Minor text updates were also made on pages 2, 5, and 6 in this version.]

an increasing demand for safer and longer-lasting dermal fillers [2]. In addition, as the market for noninvasive treatments for anti-aging expands, treatments for wrinkle improvement and facial volume restoration continue to improve [3].

Polycaprolactone (PCL) based dermal fillers were introduced to the market in 2009 as a new classification of biostimulating fillers. In the case of biostimulating fillers such as CaHA, these were shown to be superior to hyaluronic acid (HA) in the treatment of nasolabial folds, while PCL is a bioresorbable, nontoxic medical polymer that has recently been in the market spotlight for having a safe bioresorbable profile [2]. Moreover, the PCL microsphere has noncross-linking and bioresorbable properties and shows successful biocompatibility in combination with an aqueous carboxymethylcellulose (CMC) gel carrier. The PCL filler corrects wrinkles after injection due to the viscosity and microspheres of the gel carrier [3, 4]. PCL fillers are also bioabsorbent substances, which are excreted into urine through normal metabolic pathways with carbon dioxide and water. For this reason, PCL fillers have been approved as medical devices by CE certification by European and US licensing authorities for injection into the dermis and subcutaneous for wrinkle improvement [3–5].

Polynucleotides (PN) are biopolymers composed of 13 or more nucleotide monomers covalently bonded in a chain, including deoxyribonucleic acid, and ribonucleic acid. PN filler is a next-generation filler, which is used to improve skin wrinkles due to tissue repair and volume effects. Rejuran (PharmaResearch Products, Inc.) is a filler whose main ingredient consists of PN sodium based on purified PN and improves facial wrinkles. A previous clinical trial has shown that Rejuran improved crow's feet and demonstrated relatively useful efficacy and safety profiles compared to HA fillers [6].

DLMR01 (DexLevo, Inc.), is an experimental device that was used in this clinical trial, which is a novel PCL-based dermal filler (DLMR01) with those of the purified PN filler (RJR: Rejuran) in the correction of crow's feet.

2 | Materials and Methods

2.1 | Study Design

This clinical trial was designed as a randomized, participant- and evaluator-blinded, matched-pair, prospective split-face study and conducted at Chung-Ang University Hospital, Seoul, Korea. The study was approved by the Chung-Ang University Hospital institutional review board (IRB no. 2022-005-410) and written informed consent was obtained from all subjects after a full explanation of the risks and benefits of the procedure.

2.2 | Subject Selection

Healthy Asian adults (aged 19–70 years) with symmetric moderate to severe crow's feet wrinkles (2–4 points on the Crow's Feet Grading Scale (CFGS) at rest and expression) being registered. All subjects were enrolled in the study if they voluntarily signed the consent form and satisfied all of the selection and exclusion criteria. The selection criteria included that the patients had to agree not to undergo treatment that may affect their facial wrinkles during the entire study period. The exclusion criteria were for pregnant or nursing women, a history of taking antiplatelet agents within 2 weeks of the study period, a history of severe liver dysfunction or abnormal blood coagulation, treatment history of laser or wrinkle improvement therapy within 6 months of the study period, a history of applying anti-aging drugs within 3 months of the study period, having facial dermatoses, scars, or infection, and a history of hypersensitivity to PCL or PN.

2.3 | Treatment

DLMR01 composed of microparticle-free PCL was used for the experimental device. RJR (Rejuran) comprising a transparent liquid consisting of PN at a concentration of 20 mg/mL was used for the control device. For both filler injections, sterile 1.0 mL prefilled syringes with 33-gauge needles were used.

All subjects were randomized using a computer-generated code to receive a different filler injected into each crow's feet wrinkle. Topical anesthetic EMLA cream (AstraZeneca, Södertälje, Sweden) was applied 30 min before the injection if deemed necessary. The filler was injected for each area of the identified crow's feet using a linear threading technique. The amount of filler in each crow's feet area was up to 1.0 mL. All subjects and three evaluating investigators (EIs) conducted the analysis blind, whereas the treating investigator (TI) was not blinded. Re-touch treatment was not allowed.

2.4 | Clinical Assessment

Digital photographs were taken both in the rest (static) and expression (dynamic) state at every visit (at baseline (0 weeks, treatment), at 2 weeks, at 4 weeks, and at 12 weeks). The TI and 3 EI assessed the digital photographs using CFGS (0 = no wrinkles, 1 = very fine wrinkles, 2 = fine wrinkles, 3 = moderate wrinkles, and 4 = severe wrinkles). The TI and subjects assessed the Global Aesthetic Improvement Scale (GAIS) at 2, 4, and 12 weeks after treatment (−1 = worse, 0 = no change, 1 = improved, 2 = much improved, and 3 = very much improved).

The primary outcome was the improvement rate of the CFGS at rest following the assessment by the EIs at 12 weeks. An improvement was defined as when the CFGS had improved by at least one point over the treatment period. The secondary outcomes included the improvement rate of CFGS at expression, which was again assessed by the EIs at 12 weeks, the improvement rate of CFGS at rest and the expression assessed, as assessed by the EIs at 2, 4 weeks, the changes in CFGS at rest and expression, again assessed by the EIs at 2, 4, 12 weeks compared to baseline, the mean CFGS at rest and expression, assessed by the EIs at 2, 4, 12 weeks, and the mean GAIS, which was assessed by the TI and subjects at 2, 4, and 12 weeks.

2.5 | Safety Assessment

At each visit, the vital signs of the subjects were checked and physical examinations were performed. Adverse events (AEs), including erythema, pain, bruise, pruritus, heating sensation, induration, discoloration, and infections, were evaluated during the entire study period. A laboratory examination evaluated the complete blood cell count, liver function test, electrolytes, kidney function test, urine analysis, and electrocardiogram at baseline and 12 weeks.

2.6 | Statistical Analysis

All statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The efficacy and safety data are based on descriptive statistics and presented as mean ± standard deviation.

A sample size of 197 subjects was calculated to demonstrate the noninferiority of DLMR01 compared to RJR with regard to the improvement rate of CFGS at rest, as assessed by the EIs at 12 weeks, and provided a 90% power at a significance level of 2.5% and a one-sided test. After assuming a dropout rate of 10%, an enrollment of a total of 218 subjects was planned. The one-side 97.5% confidence interval of the mean intergroup difference (DLMR01–RJR) was calculated, and noninferiority was declared if the lower CI limit exceeds −10% (−0.10). The noninferiority margin was calculated based on the published clinical pilot study, which demonstrated that the improvement rate of CFGS at rest, as assessed by the EIs at 12 weeks, was 48.28% in the experimental group (DLMR01) and 41.38% in the control group (RJR) [7].

McNemar's test was performed to compare the differences in the intergroup CFGS improvement rate at rest and expression, as assessed by the EIs. Paired *t*-test and Wilcoxon's signed rank test were performed to analyze the changes in CFGS at rest and expression, as assessed by the EIs, the mean CFGS at rest and expression, again assessed by the EIs, and the mean GAIS, which was assessed by the TI and the subjects. *p*-values <0.05 were considered statistically significant for the secondary outcomes and safety profiles. Analysis of the efficacy was performed based on the full analysis set. Analysis of the safety was performed based on the safety analysis set.

3 | Results

3.1 | Demographics

A total of 218 healthy Asian subjects were enrolled and randomized in the study. Three subjects (1.38%) were applied to the filler injections after randomization but eventually dropped out because no efficacy evaluation was being conducted. Among the 215 subjects in the full analysis set, 84.19% ($n=181$) were female subjects and 15.81% ($n=34$) were male subjects. The average age of the subjects was 52.30 ± 7.03 (ranging from 35 to 67). The mean CFGS was 3.76 ± 0.43 at baseline in the experimental group and 3.74 ± 0.44 in the control group. There was no statistically significant difference in the CFGS between the experimental group and the control group at baseline. The mean injected filler amount was 0.93 ± 0.05 mL in both groups.

3.2 | Primary Outcome

The CFGS improvement rate at rest was assessed by the EIs at 12 weeks after treatment and found to be 70.23% ($n=151/215$) in the experimental group (DLMR01) and 61.40% ($n=132/215$) in the control group (RJR) (Figure 1). The improvement rate in the experimental group was 8.84% higher than in the control group. The one-side 97.5% confidence interval was −0.09% (−0.0009), which exceeded the predefined margin for noninferiority, which was −10% (−0.10). Therefore, it demonstrated the noninferiority of DLMR01 to RJR for improving crow's feet wrinkles.

3.3 | Secondary Outcome

The improvement rate of CFGS at rest was 54.93% ($n=117/215$) in the experimental group and 58.22% ($n=124/215$) in the control group at 2 weeks. The CFGS improvement rate was 55.35% ($n=119/215$) in the experimental group at rest and 58.60% ($n=126/215$) at 4 weeks. Thus, there was no statistically

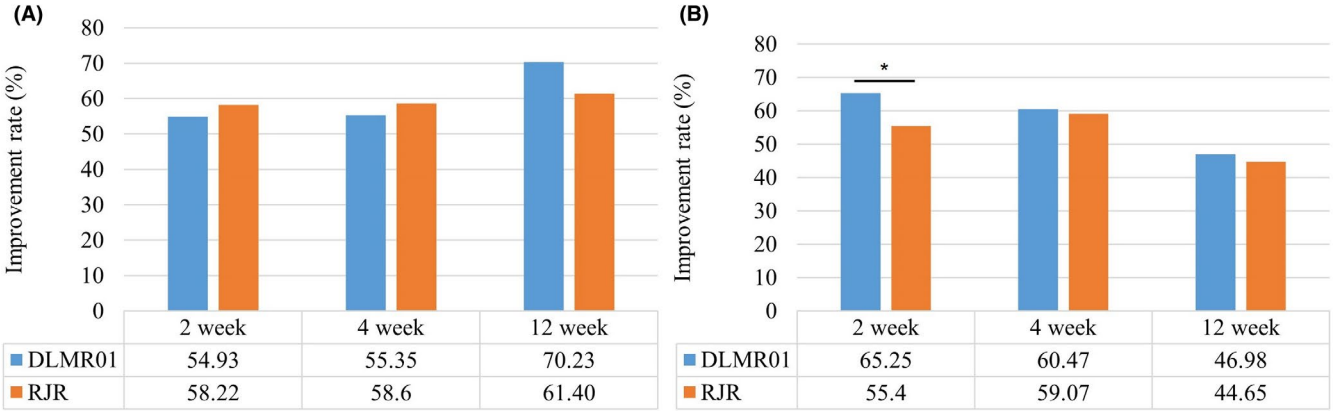

FIGURE 1 | The improvement rate of crow's feet grading scale (CFGS) at (A) rest and (B) expression assessed by blinded evaluating investigators (EIs). DLMR01, PCL-based dermal filler; RJR, Purified PN filler (Rejuran). Significant values are indicated as $*p<0.05$.

significant difference between the groups at 2 weeks ($p = 0.3778$) and 4 weeks ($p = 0.3363$).

The CFGS improvement rate at expression was 65.25% ($n = 139/215$) in the experimental group and 55.40% ($n = 118/215$) in the control group at 2 weeks, and there was a statistically significant difference between the groups (0.0103). The CFGS improvement rate at expression was 60.47% ($n = 130/215$) in the experimental group and 59.07% ($n = 127/215$) in the control group at 4 weeks. The CFGS improvement rate at expression was 46.98% ($n = 101/215$) in the experimental group and 44.65% ($n = 96/215$) in the control group at 12 weeks. Thus, there were no statistically significant differences between the groups at 4 weeks ($p = 0.7255$) and 12 weeks ($p = 0.5465$) (Figure 1).

The changes in the CFGS means between the groups were statistically significant at rest and at 12 weeks (-0.86 ± 0.70 vs. -0.73 ± 0.67, $p = 0.0015$), and in the expression at 2 weeks (-0.86 ± 0.76 vs. -0.75 ± 0.83, $p = 0.0414$). The details on the CFGS values at each visit are shown in Table 1.

The mean GAIS, assessed by the TI, showed a statistically significant difference between the groups at every following visit: at 2 weeks (2.36 ± 0.77 vs. 2.24 ± 0.79, $p < 0.0001$), at 4 weeks (2.33 ± 0.80 vs. 2.24 ± 0.79, $p = 0.0010$), and at 12 weeks (2.33 ± 0.80 vs. 2.23 ± 0.79, $p = 0.0001$). Similarly, the mean GAIS, assessed by the blinded subjects, showed a statistically significant difference between the groups at every following visit: at 2 weeks (2.42 ± 0.75 vs. 2.33 ± 0.76, $p = 0.0002$), at 4 weeks (2.41 ± 0.77 vs. 2.34 ± 0.77, $p = 0.0050$), and at 12 weeks (2.41 ± 0.76 vs. 2.35 ± 0.76, $p = 0.0106$) (Figure 2). Digital photographs of the representative subject are shown in Figure 3.

3.4 | Safety Assessments

Among the 218 subjects, 43.12% ($n = 94/218$) developed medical device-related AEs. However, most of the AEs were mild and tolerable and comprised injection site edemas, pain, bruising, pruritus, and erythema. One subject experienced induration and discoloration at the injection site, yet it was mild and disappeared spontaneously. There were no serious AEs during the entire study period. There were no clinically significant abnormalities reported in vital signs and physical examinations during the entire study period. Before treatment and at 12 weeks after treatment, there were no significant abnormalities in the laboratory examinations.

4 | Discussion

Dermal fillers have been used to improve wrinkles and increase facial volumes, while HA fillers are most frequently used for correcting facial wrinkles. Additionally, new classifications of biostimulating fillers have been introduced and their uses have been increasing due to the advantage of a longer duration of action. PCL-based dermal fillers have demonstrated long-lasting volumizing and rejuvenating effects on nasolabial folds, foreheads, and hands [5, 8, 9]. Classic PCL-based dermal fillers contain PCL microspheres, which are suspended in a gel carrier and subsequently biodegraded through a slow hydrolytic process. PCL fillers can immediately provide volumizing effects to facial volume deficit areas and have sustained effects as a collagen stimulator. In this study, the investigator-assessed improvement rate was the best on the DLMR01 side after 12 weeks of treatment, which is thought to be due to the collagen-stimulating effect. In a previous human study, neocollagenesis was observed 13 months after PCL filler injection [10].

TABLE 1 | Crow's feet grading scale assessed by blinded evaluating investigators (total $n = 215$).

		DLMR01	RJR	DLMR01—RJR	*p*
At rest	0 week (Baseline)	3.76 ± 0.43	3.74 ± 0.44	0.02 ± 0.35	0.4436
	2 weeks	2.97 ± 1.04	2.89 ± 1.09	0.08 ± 0.91	0.1539
	4 weeks	2.94 ± 1.09	2.92 ± 1.06	0.02 ± 0.84	0.6837
	12 weeks	2.90 ± 0.80	3.01 ± 0.83	-0.12 ± 0.54	0.0010*
At rest	2 weeks–0 weeks	-0.79 ± 0.91	-0.85 ± 0.92	0.07 ± 0.92	0.2467
	4 weeks–0 weeks	-0.82 ± 0.95	-0.82 ± 0.90	0.00 ± 0.85	0.9189
	12 weeks–0 weeks	-0.86 ± 0.70	-0.73 ± 0.67	-0.13 ± 0.65	0.0015*
At expression	0 weeks (Baseline)	3.87 ± 0.33	3.88 ± 0.32	-0.01 ± 0.32	0.6800
	2 weeks	3.02 ± 0.82	3.14 ± 0.87	-0.12 ± 0.81	0.0252*
	4 weeks	3.05 ± 0.86	3.12 ± 0.82	-0.07 ± 0.82	0.2700
	12 weeks	3.34 ± 0.71	3.36 ± 0.71	-0.02 ± 0.58	0.5622
At expression	2 weeks–0 weeks	-0.86 ± 0.76	-0.75 ± 0.83	-0.11 ± 0.82	0.0414*
	4 weeks–0 weeks	-0.82 ± 0.79	-0.77 ± 0.76	-0.06 ± 0.85	0.3501
	12 weeks–0 weeks	-0.53 ± 0.65	-0.52 ± 0.66	-0.01 ± 0.60	0.7353

Abbreviations: DLMR01, PCL-based dermal filler; RJR, purified PN filler (Rejuran).
*$p < 0.05$.

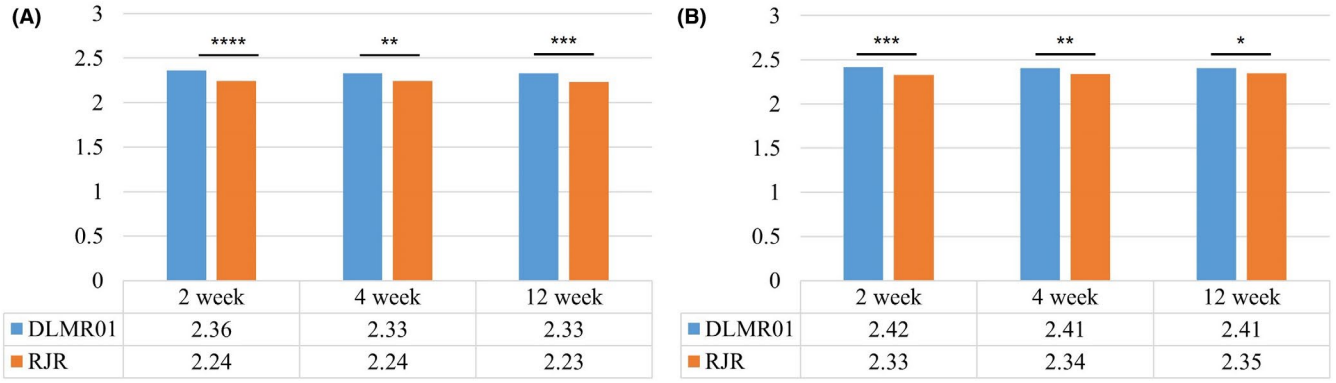

FIGURE 2 | Global Aesthetic Improvement Scale (GAIS) assessed by (A) treating investigator (TI) and (B) blinded subjects DLMR01, PCL-based dermal filler; RJR, Purified PN filler (Rejuran). Significant values are indicated as $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$.

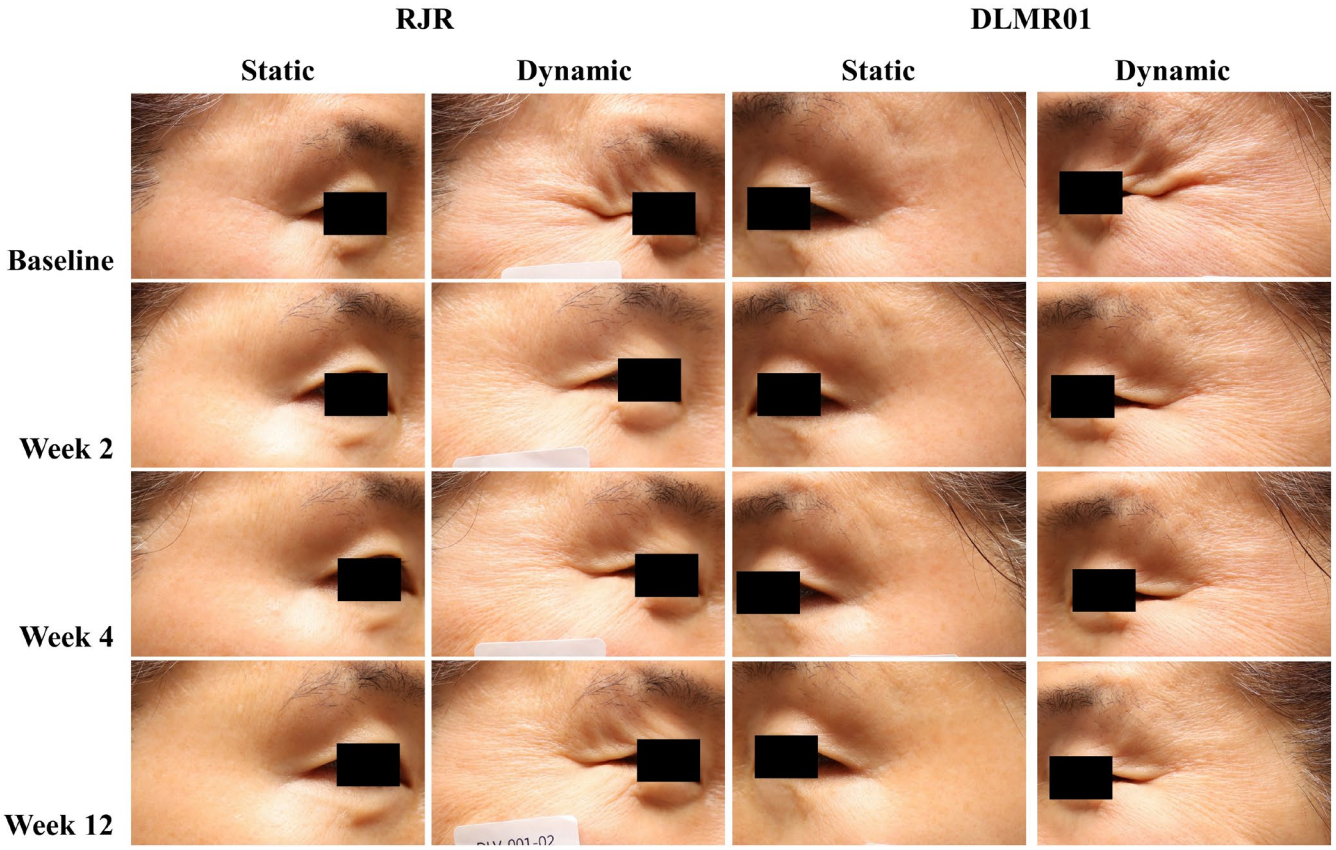

FIGURE 3 | Clinical photographs of representative subjects showing improvements in crow's feet wrinkle at rest and expression after treatment. DLMR01, PCL-based dermal filler; RJR, Purified PN filler (Rejuran). The crow's feet grading scale scores were as follows; RJR Static: 3 point (Baseline), 1 point (Week 2), 2 point (Week 4), and 2 point (Week 12). RJR Dynamic: 3 point (Baseline), 2 point (Week 2), 2 point (Week 4), and 2 point (Week 12). DLMR01 Static: 3 point (Baseline), 3 point (Week 2), 2 point (Week 4), and 2 point (Week 12). DLMR01 Dynamic: 4 point (Baseline), 3 point (Week 2), 2 point (Week 4), and 2 point (Week 12).

The conventional PCL filler is a high-viscosity filler whereby solid PCL is dispersed in an aqueous CMC solution, thereby providing a viscosity that ranges from 180 to 230 Pas. The maintenance period is usually 1–2 years, although PCL fillers, which last up to 4 years, have been recently released [9]. Alternatively, the main material in DLMR01, the experimental device used in this clinical trial, was PCL. It was confirmed that pegylation technology has been used consistently in the medical polymer field, and that PCL is also a biodegradable polymer. The other ingredient of DLMR01 is PEG. PEG has excellent biocompatibility and is actively used in the biomedical field in combination with various functional groups [14]. The advantage of DLMR01, composed of PCL and PEG, is their low viscosities (ranging from 0.1 to 0.9 Pas). Moreover, unlike general PCL fillers, which have high viscosities and can only be injected into the deep subcutaneous layer of the skin, DLMR01 can be injected into the relatively superficial skin layer due to its low viscosity.

Our results showed that for dynamic wrinkles, DLMR01 achieved its maximum effect 2 weeks after the procedure, while RJR reached its maximum effect 4 weeks after the procedure. Due to this difference in the timing of maximum effects, only the improvement in CFGS at expression at 2 weeks showed statistical significance when comparing the two groups. We suggested that the differences in biocompatibility and viscosity between pegylated PCL and conventional PLC might explain why the maximum effect at expression is achieved slightly earlier with DLMR01. However, it was confirmed that both treatments showed similar effects at expression at the 12-week follow-up.

One limitation of this study is the short study period of 12 weeks. This is because past clinical trials using RJR, as a control in this study, have used a 12-week posttreatment observation period [7, 16]. Future studies should include a longer follow-up period of 12 months or more with other control fillers.

In this clinical trial, a randomized, and evaluator-blinded study was conducted to confirm the crow's feet correction effect of newly developed PCL-fillers compared to PN fillers using a large number of subjects. The CFGS improvement rate (decrease of at least 1 point in CFGS compared to baseline) at rest and at 12 weeks after PCL filler was 70.23%, and we confirmed that DLMR01 is noninferior to RJR in improving crow's feet wrinkles. Additionally, the changes in the mean CFGS at 12 weeks compared to the baseline in the DLMR01 group were significantly higher than in the RJR group. For safety assessment, there were no severe AEs and both fillers showed good safety profiles.

In conclusion, DLMR01 can be an effective and safe dermal filler option for improving crow's feet wrinkles. To investigate the prolonged efficacy and safety of new PCL dermal fillers, further long-term, randomized, blinded, prospective, split-face studies would be recommended.

Acknowledgments

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Ethics Statement

This study's protocol was approved by the Institutional Review Board of Chung-Ang University Hospital (IRB Approval No. 2022-005-410). All participants signed a photo release consent form authorizing the reproduction and distribution of any images collected during the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, BJK, upon reasonable request.

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[Correction added on 13 January 2025, after first online publication: References 11, 12, 13, and 15 has been removed in this version.]