

Safety and effectiveness of hyaluronic acid fillers in skin of color

Pearl E Grimes, MD,¹ Jane A Thomas, AAS, CCRA,² & Diane K Murphy, MBA²

¹Vitiligo and Pigmentation Institute of Southern California, Los Angeles, CA, USA

²Allergan, Santa Barbara, CA, USA

Summary

Objectives To assess the safety and effectiveness of hyaluronic acid (HA) fillers in skin of color.

Methods Two prospective studies followed up subjects with Fitzpatrick skin phototypes of IV, V, or VI for 24 weeks after dermal filler injections. In a double-blind, randomized study, subjects were injected with one of three high concentration (24 mg/mL) HA fillers (Juvéderm Ultra, Ultra Plus, and 30) in one nasolabial fold and Zyplast collagen in the other. In an open-label, randomized study, subjects received one of three low concentration (5.5 mg/mL) HA fillers (Hylaform, Hylaform Plus, and Captique) in both nasolabial folds.

Results A total of 160 subjects (a subset of 439 study subjects) were randomized and treated with one of the three high concentration fillers, and 119 subjects were randomized and treated with one of the three low concentration fillers. For subjects treated with the high concentration fillers there were no occurrences of hypersensitivity or hypertrophic scarring, and no increased incidence of hyperpigmentation or hypopigmentation in non-Caucasian vs. Caucasian subjects. For subjects treated with the low concentration fillers there were no occurrences of keloid formation, hypertrophic scarring, hypopigmentation, hypersensitivity, and three instances of mild hyperpigmentation. For all of the fillers the majority of subjects maintained ≥ 1 point improvement in nasolabial fold severity scores through 24 weeks.

Conclusions All of the HA fillers were well tolerated in individuals with skin of color and demonstrated effectiveness throughout the 24 week period. Furthermore, the fillers provided smooth, natural-looking wrinkle correction in darker skin types.

Keywords: dermal filler, wrinkles, skin of color, hypertrophic scars, keloid, hyperpigmentation

Introduction

An awareness of the characteristic defining traits in skin of color is necessary for successful facial rejuvenation of the darker-skinned patient. The increased level of epidermal melanin in darker skin confers advantages in that its photoprotective nature reduces

the risk of skin cancer and photodamage to the skin.^{1–6} It carries disadvantages, however, because it makes the skin more reactive to stimuli, and thus susceptible to postinflammatory dyspigmentation.^{1,2,4–7} Skin of color, particularly black skin, is also predisposed to hypertrophic or keloidal scarring.^{1,5–10} Due to these characteristics of darker skin, it is important to determine whether the theoretically greater potential for adverse events from dermal filler injections is demonstrated in clinical practice. To investigate this issue, we present the results of two studies examining the safety and

Correspondence: Pearl E Grimes, 5670 Wilshire Blvd., Suite 650, Los Angeles, CA 90036. E-mail: pegrimesmd@earthlink.net

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effectiveness of hyaluronic acid (HA) fillers in darker skin.

Methods

Study design

Two prospective, multi-center U.S. trials examined the safety and effectiveness of HA fillers for correction of nasolabial folds (NLFs). One trial was a double-blind, randomized clinical study of Juvéderm® Ultra, Juvéderm® Ultra Plus, and Juvéderm® 30 (Allergan, Santa Barbara, CA, USA) at 11 sites. Subjects were randomized to receive up to three bilateral treatments (initial treatment and two touch-ups at 2 week intervals) of a Juvéderm product in one NLF and Zyplast® bovine collagen (Allergan) in the other. Follow-up physician assessments of safety and effectiveness occurred at 2, 4, 8, 12, 16, 20, and 24 weeks after the last treatment. Subjects also assessed safety via diaries for 14 days after each treatment. Overall study results have previously been reported;^{11,12} the results herein focus solely on the skin of color subset population.

The second trial was an open-label, randomized study to ascertain the safety of Hylaform®, Hylaform® Plus, and Captique® (Allergan). Subjects received a single treatment of one of the HA fillers in both NLFs, with no touch-up injections allowed. Follow-up safety assessments for the incidence rates of keloid formation, hypertrophic scarring, hyperpigmentation, hypopigmentation, and symptoms of potential hypersensitivity occurred at 2, 4, 12, and 24 weeks posttreatment. Effectiveness was assessed for the subjects at one of the three investigational sites.

Both studies also included serum IgG antibody testing as an indicator of immunological response to the HA, with blood samples collected at baseline, 4, and 12 weeks (Hylaform/Captique) or 24 weeks (Juvéderm). An increase greater than fourfold from baseline in serum IgG antibody titer was considered a positive response.

Subjects

Subjects in the Juvéderm study were included if they were >30 years of age, with bilateral NLFs that were approximately symmetrical with severity scores of 2 or 3 on the 5-point photographic Wrinkle Assessment Scale (WAS; range 0–4). Subjects in the Hylaform/Captique study were included if they were ≥18 years of age and had Fitzpatrick skin phototype IV, V, or VI. Exclusion criteria were similar for both

studies and included hypersensitivity to product materials or severe allergies, permanent facial implants, or facial cosmetic procedures within 6 months of study entry. All subjects signed informed consent, and the study protocols were approved by institutional review boards.

Materials

All of the HA fillers are FDA-approved for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds and are sterile, nonpyrogenic, viscoelastic gels. The Juvéderm products are formulated to an HA concentration of 24 mg/mL produced by *Streptococcus equi* bacteria. The other fillers have an HA concentration of 5.5 mg/mL and are derived from either an avian (Hylaform and Hylaform Plus) or *Streptococcus zooepidemicus* bacterial (Captique) source.

Results

Demographics

Subjects were randomized to treatment product in a 1:1:1 ratio in both studies, with 160 subjects in the Juvéderm study and 119 in the Hylaform/Captique study. The vast majority of subjects completed the 6-month study period (91–100% for the Juvéderm cohorts; 95–100% for the Hylaform/Captique cohorts).

Subjects were predominantly female with a median age of 50 years for Juvéderm and 53 years for Hylaform/Captique. Skin phototype IV was the most common (56%) for Juvéderm subjects, whereas phototype V was the most common (47%) in the Hylaform/Captique groups (Table 1).

The total median injection volume for the initial treatment plus touch-ups of a single NLF was 1.6 mL for each of the Juvéderm formulations. Median injection volume for the single bilateral NLF treatment was 2.3 mL for Hylaform, 1.6 mL for Hylaform Plus, and 2.0 mL for Captique.

Safety

For the Juvéderm fillers, side effects were localized to the treatment site and consisted primarily of pain, swelling, redness, induration, and nodules. No hypertrophic scarring or keloid formation occurred, and there was no increased incidence of hyperpigmentation or hypopigmentation in non-Caucasian vs. Caucasian subjects. Pigmentation changes were recorded on subject diaries

Table 1 Demographic data

Characteristic	Juvéderm Ultra (N = 53)	Juvéderm Ultra Plus (N = 53)	Juvéderm 30 (N = 54)	Hylaform (N = 39)	Hylaform Plus (N = 41)	Captique (N = 39)
Median age (years)	50	49	49	55	53	53
Range	32–75	26–74	34–64	37–71	32–69	34–77
Gender (%)						
Female	91	87	96	90	98	97
Male	9	13	4	10	2	3
Phototype, n (%)						
IV	24 (45)	31 (58)	34 (63)	15 (39)	7 (17)	10 (26)
V	24 (45)	18 (34)	15 (28)	13 (33)	24 (59)	19 (49)
VI	5 (9)	4 (8)	5 (9)	11 (28)	10 (24)	10 (26)

as “discoloration (not redness or bruising),” and many of these reports lasted just a day or two. There were 12 reports (7.5%) of discoloration lasting >10 days in non-Caucasian subjects, and all resolved without sequelae before study end.

For the Hylaform and Captique fillers, there were no occurrences of keloid formation, hypertrophic scarring, hypopigmentation, or symptoms of hypersensitivity. Three subjects (2.5%) developed mild cases of hyperpigmentation. Injection site reactions, including bruising, nodules, and pain, were predominantly mild and short-lasting (≤ 7 days).

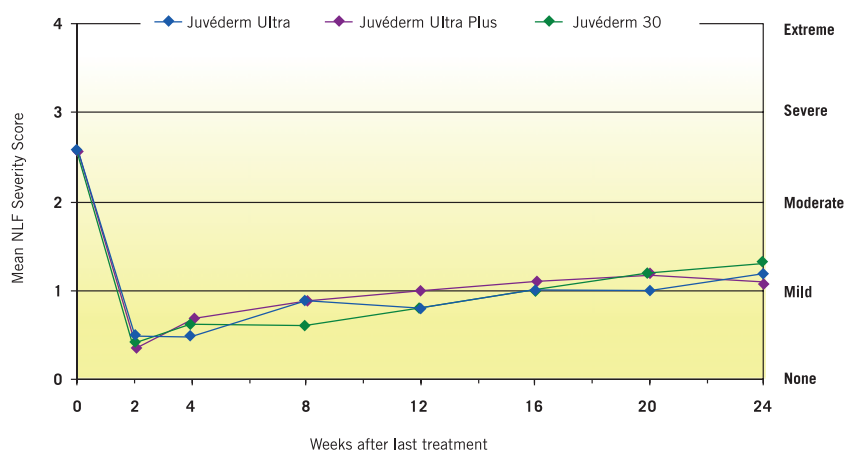
None of the Juvéderm subjects exhibited a positive IgG antibody titer at 4 weeks posttreatment. One subject had a positive titer at 24 weeks that was not associated with any clinical symptoms. None of the subjects from the Hylaform/Captique study demonstrated a positive antibody response.

Effectiveness

The mean NLF severity scores at baseline on the 5-point WAS were 2.6 for both Juvéderm Ultra and Ultra Plus, and

2.5 for Juvéderm 30 (Fig. 1). At 2 weeks after the last treatment, the mean severity score had improved by ≥ 2 points in all cohorts, to 0.6 for Juvéderm Ultra, 0.4 for Juvéderm Ultra Plus, and 0.5 for Juvéderm 30 and 0.5–0.7 for Zyplast NLFs. By the end of the 6-month study period, the improvement was still clinically significant (≥ 1 point) for all three Juvéderm products, with mean improvement of 1.3 for Juvéderm Ultra, 1.5 for Juvéderm Ultra Plus, and 1.2 for Juvéderm 30 but not significant for the Zyplast NLFs with mean improvement of 0.4–0.5. The vast majority of subjects (> 80%) maintained ≥ 1 point improvement in NLF severity through 24 weeks (Fig. 2), with natural-looking correction (Fig. 3).

All 40 subjects at the senior author's (P.E.G.) site underwent effectiveness evaluations, and the mean NLF severity scores at baseline on the 6-point Genzyme wrinkle scale were 3.3 for Hylaform, 2.9 for Hylaform Plus, and 3.3 for Captique (Fig. 4). At 2 weeks after treatment, the mean severity score for all cohorts had improved by ≥ 2 points to 1.0 for Hylaform, 0.6 for Hylaform Plus, and 0.9 for Captique. By the end of the 6-month study, the mean severity score was 2.7 for Hylaform, 2.1 for Hylaform Plus, and 2.9 for Captique. The majority of subjects

**Figure 1** Mean nasolabial fold severity scores assessed by investigator.

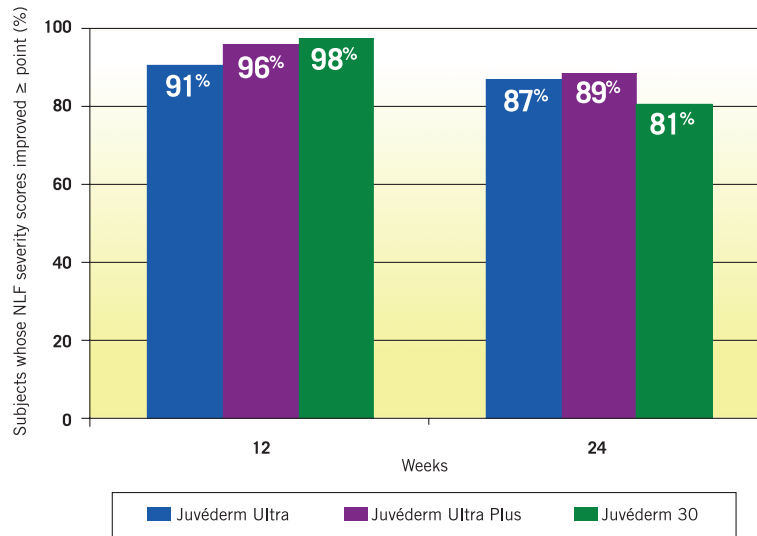


Figure 2 Percentage of subjects with improved nasolabial fold severity scores from baseline based on investigator assessment.



Figure 3 Nasolabial folds at 2 and 24 weeks postinjection.

(>60%) maintained ≥ 1 point improvement in NLF severity through 24 weeks (Fig. 5) with a single injection. Although the sample size is small for the effectiveness

evaluation ($N = 14, 17$, and 9 in the Hylaform, Hylaform Plus, and Captique groups, respectively), the results provide insight into longevity of the correction (Fig. 3).

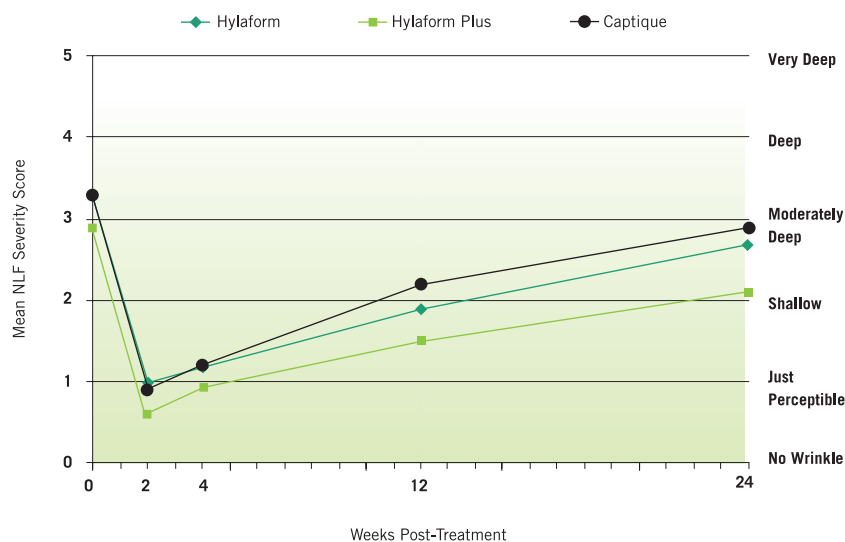


Figure 4 Mean nasolabial fold severity scores assessed by investigator.

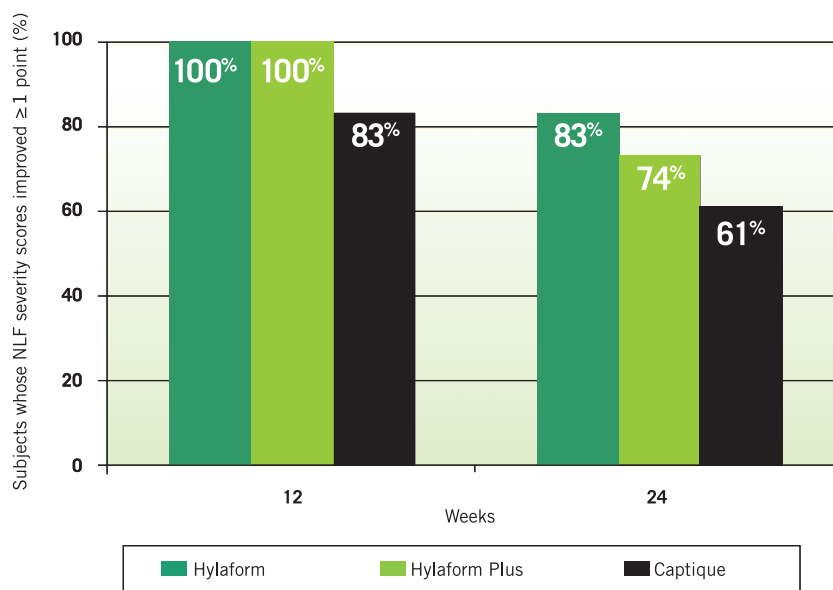


Figure 5 Percentage of subjects with improved nasolabial fold severity scores from baseline based on investigator assessment.

Discussion

This study investigated the safety and effectiveness of various HA dermal fillers in subjects with Fitzpatrick skin phototypes IV–VI. The results demonstrate that HA fillers are well tolerated in skin of color, with natural-looking correction lasting at least 3–6 months. Furthermore, side effects were mild, temporary, and localized to the injection site.

At 24 weeks posttreatment, >80% of subjects in the Juvéderm groups maintained a ≥ 1 -point improvement in

NLF severity and mirrored the results of subjects with Fitzpatrick skin phototypes I–III.¹³ At 24 weeks, subjects with skin of color had NLF severity scores of 1.1–1.3, compared with 1.2–1.4 for the Caucasian subjects. Hypertrophic scarring or keloid formation did not occur, nor was there an increased incidence of hyperpigmentation or hypopigmentation between lighter and darker-skinned subjects.

At 24 weeks posttreatment, >60% of subjects in the Hylaform, Hylaform Plus, and Captique study maintained ≥ 1 point improvement in NLF severity. No instances of

keloidal scarring or hypersensitivity were reported, and the occurrence of mild hyperpigmentation was similar to that expected in a skin of color population.

Limited published data describe the safety and effectiveness of HA fillers in skin of color. Grimes and Few previously found a 6% incidence of postinflammatory hyperpigmentation at the injection site, which resolved with topical steroids and 4% hydroquinone.¹ Odunze *et al.* found no transient or permanent adverse outcomes among Fitzpatrick skin phototype IV–VI subjects using HA fillers,¹⁴ and Taylor and Burgess found pigmentation changes in 15% of patients, which resolved within 12 weeks.¹⁵

Meticulous technique with minimal blood accumulation is essential for reducing complications when using HA fillers in darker skin types. The current studies demonstrate that patients with Fitzpatrick skin phototypes IV–VI may be effectively and safely treated for the correction of facial wrinkles and folds with HA fillers, thus delaying the need for surgery and the propensity for scarring.

While our studies demonstrated that all of the HA fillers can be safely and effectively used in individuals with darker skin, the duration of the wrinkle correction is linked to the physical properties of the fillers.¹⁶ The Juvéderm fillers, with a higher concentration of HA and higher concentration of crosslinked HA,¹¹ would be expected to last longer *in vivo* than the Hylaform and Captique fillers, which have a lower concentration of HA and lower concentration of crosslinked HA.¹⁷ In fact, this has been found to be the case in practice, with Hylaform and Hylaform Plus lasting 3–4 months and Captique lasting 3–6 months¹⁸ while the Juvéderm fillers last from 9 months to a year or more.¹²

Conclusions

The HA fillers were effective and well tolerated in skin of color, with no occurrences of hypertrophic or keloidal scarring or hypersensitivity, and no increased incidence of hyperpigmentation or hypopigmentation compared to Caucasian skin. The fillers provided smooth, natural-looking, and long-lasting wrinkle correction and a good safety profile in persons with darker skin types.

Conflicts of interest

Dr. Grimes is an investigator for Allergan. Ms. Thomas and Ms. Murphy are Allergan employees and stockholders.

Acknowledgments

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