Combining Microfocused Ultrasound With Botulinum Toxin and Temporary and Semi-Permanent Dermal Fillers: Safety and Current Use

Sabrina G. Fabi, MD,* Mitchel P. Goldman, MD,* Daniel C. Mills, MD,† W. Philip Werschler, MD,‡ Jeremy B. Green, MD,§ Joely Kaufman, MD,§ Robert A. Weiss, MD,‖ and Carl S. Hornfeldt, PhD¶

BACKGROUND A microfocused ultrasound system with visualization (MFU-V) is currently indicated for use as a noninvasive dermatological aesthetic treatment to lift the eyebrows, lax submental and neck tissue, and improve lines and wrinkles of the décolleté.

OBJECTIVE To determine the existence of any safety signals when combining MFU-V with botulinum toxin-A and/or semipermanent and temporary dermal fillers.

MATERIALS AND METHODS A retrospective chart review was performed using subjects who received aesthetic treatments including incobotulinumtoxinA injection, cohesive polydensified matrix hyaluronic acid (CPM HA) dermal fillers, and calcium hydroxylapatite (CaHA) dermal fillers within 6 months of treatment with MFU-V in the same or different anatomic areas.

RESULTS All subjects (N = 101; 96 female; 25–70 year old) received MFU-V, 18% received incobotulinumtoxinA injections, and 81% were treated with CPM HA and/or CaHA fillers. Seven adverse events (7%) were reported: bruising/purpura (n = 4), swelling (n = 1), paresthesia (n = 1), and herpes simplex virus (HSV) outbreak (n = 1). Only the HSV outbreak was considered to be related to combined treatments.

CONCLUSION Although limited by relatively few subjects, the results of the present study suggest that the safety profile of MFU-V combined with other aesthetic products is consistent with the safety profiles of the individual treatments.

This study was sponsored by Ulthera, Inc.; Mesa, AZ; and Merz GmbH, Frankfurt, Germany. S. G. Fabi is a consultant and researcher, Merz Pharmaceuticals. W. P. Werschler has served as a clinical investigator, consultant for Merz. M. P. Goldman performs research for Ulthera/Merz, Allergan, and Galderma. R. A. Weiss is a consultant and serves on the advisory board for Merz Pharmaceuticals. The remaining authors have indicated no significant interest with commercial supporters.

A microfocused ultrasound system is currently indicated for use as a noninvasive dermatological aesthetic treatment to lift the eyebrows, lax submental and neck tissue, and improve lines and wrinkles of the décolleté (Ulthera System; Ulthera, Inc., Mesa, AZ).[1] This device is used in conjunction with an imaging transducer (microfocused ultrasound system with visualization [MFU-V]) that enables ultrasonic visualization of depths up to 8 mm below the surface of the skin (Ulthera DeepSEE Transducer; Ulthera, Inc.). Ultrasound imaging ensures proper coupling of the transducer to the skin and confirms appropriate depth of treatment, avoiding nontarget tissue, such as bone. This device was recently acquired by Merz Pharma GmbH.

Merz Pharma GmbH also markets several aesthetic products including a botulinum toxin

*Dermatology Cosmetic Laser Medical Associates of La Jolla, San Diego, California; †Aesthetic Plastic Surgical Institute, Laguna Beach, California; ‡Premier Clinical Research, Spokane, Washington; §Skin Associates of South Florida, Coral Gables, Florida; ‖Maryland Laser Skin and Vein Institute, Hunt Valley, Maryland; ¶Apothekon Inc., Woodbury, Minnesota

ISSN: 1076-0512 • Dermatol Surg 2016;42:S168–S176 • DOI: 10.1097/DSS.0000000000000751

(incobotulinumtoxinA) indicated for the temporary improvement of the appearance of moderate-to-severe glabellar lines associated with corrugator and/or procerus muscle activity in adults[2]; a cohesive polydensified matrix hyaluronic acid dermal filler (CPM HA) indicated for injection into the mid-to-deep dermis for correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds[3]; and a calcium hydroxylapatite dermal filler (CaHA) indicated for subdermal implantation for the correction of moderate-to-severe facial wrinkles and folds, such as nasolabial folds and also intended for restoration and/or correction of the signs of lipoatrophy in people with human immunodeficiency virus.[4]

Many physicians combine aesthetic products and energy-emitting devices to achieve 3-dimensional facial rejuvenation and optimal aesthetic results[5–14]; however, the safety of combining MFU-V with other aesthetic products has not been evaluated. Limited clinical data exist on combining MFU-V with injectable products or multiple treatment modalities. The primary objective of this study was to determine the existence of any safety signals for MFU-V when used within 6 months of treatment (before or after) with the Merz line of aesthetic products (incobotulinumtoxinA injection, CPM HA, or CaHA dermal fillers). The use of other aesthetic products or procedures within 6 months of MFU-V treatment was also captured.

Methods

Study Subjects

A retrospective chart review was performed at 5 US study sites. Healthy men and women who were 25 to 70 year old and had received treatment with incobotulinumtoxinA injection, CPM HA, or CaHA dermal fillers within 6 months of treatment with MFU-V during a 2-year period were included. Qualifying treatment combinations were limited to MFU-V treatment of the face and/or neck with incobotulinumtoxinA and/or dermal fillers (CPM CA/CaHA) administered in the same, adjacent, or separate areas; in addition, the use of other products in this subject population was also reviewed. The chart review included identification of high-quality 2- or 3-dimensional before-and-after digital images with consistent lighting, focus, and subject positioning for possible publication purposes. Images from approximately 5 subjects were collected at each study site.

Ethics

Subjects with eligible photographs were chosen and contacted to obtain authorization for permission to use before releasing them to the study sponsor. This chart review was conducted in accordance with the Protection of Human Subjects Regulations, including Subpart B Authorization to disclose photographs of Human Subjects (21 CFR Part 50), the Institutional Review Board Regulations (21 CFR Part 56), and the Financial Disclosure by Clinical Investigators Regulations (21 CFR Part 54). This study was approved by a commercial institutional review board (Asentral IRB, Newburyport, MA; ClinicalTrials.gov Identifier NCT02444169).

Primary Outcome Measure

The primary goal of the study was to determine the existence of any safety signals when MFU-V is used within 6 months of other filler or toxin treatments. The primary outcome measure was the number of reported adverse events (AEs) associated with the use of incobotulinumtoxinA, CPM HA, and/or CaHA within 6 months before or after treatment with MFU-V.

Statistical Analysis

Data were summarized using descriptive statistics for each time point for which data were available. Subjects with incomplete data were included in summaries for which data were available. Categorical variables were summarized as frequencies. Continuous and ordinal variables were summarized as the number of subjects, means, standard deviations, medians, and ranges. Adverse events were presented as the number of subjects reporting each event.

Results

The final study population ($N = 101$) included 4 male and 96 female subjects with a mean age of 55.3 years (range, 32–72 years) (gender not reported for

1 subject). All subjects were treated with MFU-V over the full face (n = 48; 48%), the neck (n = 58; 57%), and/or décolleté (n = 7; 7%) (some subjects were treated in more than 1 area). Forty-five subjects (45%) received partial facial treatments or treatment to other areas including the lower face (n = 25), perioral region (n = 11), periorbital region (n = 7), cheeks (n = 3), upper face (n = 3), jawline and chin (n = 2), lower eyelids (n = 2), brows (n = 2), chest (n = 1), submentum (n = 1), and lip (n = 1). Transducers with treatment depths of 4.5 mm (n = 84), 3.0 mm (n = 99), and 1.5 mm (n = 69) were used to treat underlying muscles/superficial muscular aponeurotic system (n = 92), dermis (n = 87), subcutaneous tissue (n = 54), and septae (n = 53).

Seven subjects received MFU-V without premedication for treatment discomfort, while the remaining subjects received one or more pretreatment medications (Table 1). Two subjects received reduced energy treatments because of treatment discomfort.

Among the 101 subjects treated with MFU-V, 81 (81%) received CPM HA/CaHA dermal fillers, 18 (18%) received incobotulinumtoxinA, and 2 (2%) received incobotulinumtoxinA and either CPM HA or CaHA dermal fillers. Most other treatments occurred within 90 days of administration of MFU-V (Table 2).

Six subjects received a second MFU-V treatment, from 62 to 446 days after the first treatment. Second MFU-V treatments were administered over the full face (n = 4), neck (n = 4), and décolleté (n = 2); partial facial treatments to the perioral (n = 1) and periorbital areas (n = 1) were also administered. All subjects receiving second treatments received one or more pretreatment medications (Table 1). Two of these subjects were treated with CaHA (n = 1) and CPM HA (n = 1) on the same day.

TABLE 1. Pretreatment Medications

	Subjects, n
Treatment 1	
Topical anesthetic	52
Ibuprofen 800 mg	36
Alprazolam 0.25–1 mg	30
Diazepam 20 mg	20
Oxycodone 5 mg/acetaminophen 325 or 500 mg	16
Lorazepam 1 or 1.5 mg	13
Meperidine 25–100 mg IM	13
Ketorolac 30 or 60 mg IM	12
Hydrocodone 7.5 or 10 mg/ acetaminophen 325 mg	9
Acetaminophen 325 or 1,000 mg	8
Hydroxyzine 50 mg IM	7
Promethazine 25–50 mg IM	6
Hydrocodone 10 mg	3
Tramadol 37.5 mg/acetaminophen 325 mg 1 or 2 tablets	2
General anesthesia	2
Unknown	1
None	7
Treatment 2	
Ibuprofen 800 mg	2
Lorazepam 1 mg	2
Hydrocodone 7.5 mg/acetaminophen 325 mg	2
Oxycodone 5 mg/acetaminophen 325 mg	2
Topical anesthetic	2
Toradol 60 mg IM	2
Diazepam 5 mg	2
General anesthesia	1

IM, intramuscular.

IncobotulinumtoxinA Treatments

The 20 subjects treated with incobotulimuntoxinA were injected in the periocular area (n = 16), glabella (n = 14), neck (n = 10), forehead (n = 9), submentum (n = 1), and masseters (n = 1); 19 subjects received injections in multiple areas. The dose of incobotulinumtoxinA ranged from 5 to 50 U per treated area with most subjects receiving 15 to 30 U. Targets for incobotulinumtoxinA injections included muscle (n = 48) and intradermal areas (n = 10). A subject who received incobotulinumtoxinA in the forehead, glabella, and periocular areas after MFU-V is shown in Figures 1A,B and 2A,B. A patient who received incobotulinumtoxinA in the forehead, glabella, and periocular areas approximately 2 months after MFU-V is shown in Figures 3A,B and 4A,B. Seven subjects were also treated with types of dermal fillers (n = 7), intense pulsed light (n = 1), and laser resurfacing (n = 1). Four subjects received MFU-V on the same day as the incobotulinumtoxinA treatment.

TABLE 2. Time Between MFU-V and Other Therapies

	Days Before MFU-V					*Day After MFU-V*					
	180–90	*89–30*	*29–14*	*13–7*	*1–6*	*0*	*1–6*	*7–13*	*14–29*	*30–89*	*90–180*
CPM HA CaHA	9	10	3	2	1	16	0	0	2	13	13
IncobotulinumtoxinA	2	1	0	0	1	4	0	1	1	5	2

Five subjects received a second incobotulinumtoxinA treatment to the periocular area ($n = 5$), glabella ($n = 2$), and forehead ($n = 2$). The doses of incobotulinumtoxinA administered during the second treatment varied from 4 to 30 U per area. Other treatments performed on 2 subjects during the same visit as the second incobotulinumtoxinA treatment included laser resurfacing ($n = 2$) and another type of dermal filler ($n = 1$). Four subjects received a third incobotulinumtoxinA treatment to the glabella ($n = 1$), forehead ($n = 2$), and neck ($n = 1$), and 1 was treated with another type of dermal filler.

Filler (Cohesive Polydensified Matrix Hyaluronic Acid/Calcium Hydroxylapatite) Treatments

The 83 subjects treated with a dermal filler received CPM HA ($n = 57$; 69%) or CaHA ($n = 26$; 31%) in the following areas: perioral ($n = 47$), periocular ($n = 22$), cheeks ($n = 22$), temples ($n = 9$), chin ($n = 5$), nasolabial folds ($n = 3$), neck ($n = 2$), jawline ($n = 2$), tear trough ($n = 2$), lateral face ($n = 2$), glabella ($n = 1$), corner of lips ($n = 1$), marionettes ($n = 1$), preauricular ($n = 1$), scars on chin ($n = 1$), and prejowl sulcus ($n = 1$). Most subjects received injections in more than one area.

The volume of CPM HA dermal filler injected ranged from 0.3 to 2.0 mL, with most subjects receiving 1.0 mL. The volume of CaHA dermal filler injected ranged from 0.8 to 4.5 mL, with most receiving 1.5 mL. Target areas included intradermal ($n = 59$), subdermal ($n = 56$), and supraperiosteal tissues ($n = 11$). Additional treatments were performed in 41 subjects at the same time as their CPM HA/CaHA treatment. These included onabotulinumtoxinA injections ($n = 18$), other types of dermal fillers ($n = 16$), laser resurfacing ($n = 3$), intense

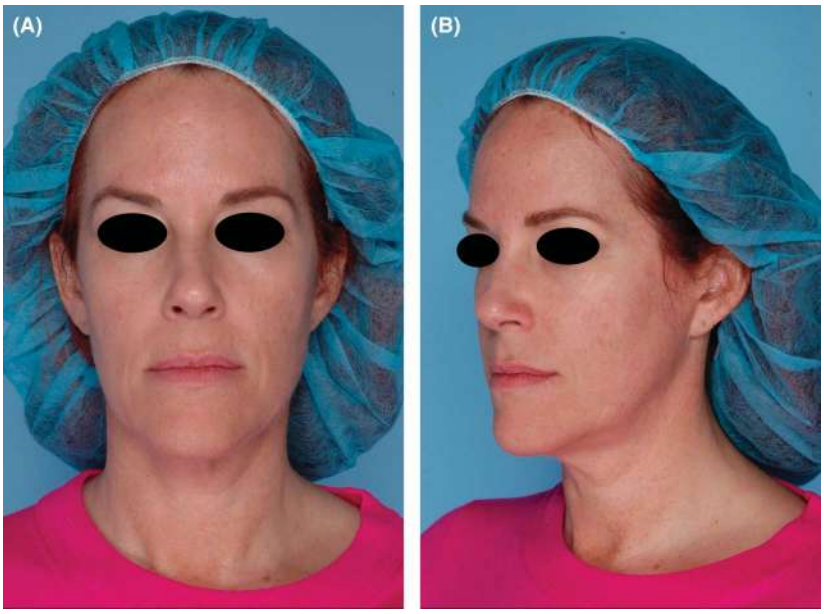

Figure 1. (A and B) This subject underwent partial face (perioral) MFU-V treatment with all transducer depths using topical anesthesia and ibuprofen as pretreatment medications. These images were obtained 53 days earlier. The patient subsequently received onabotulinumtoxinA after 42, 116, and 184 days to the glabella, forehead, and periocular regions.

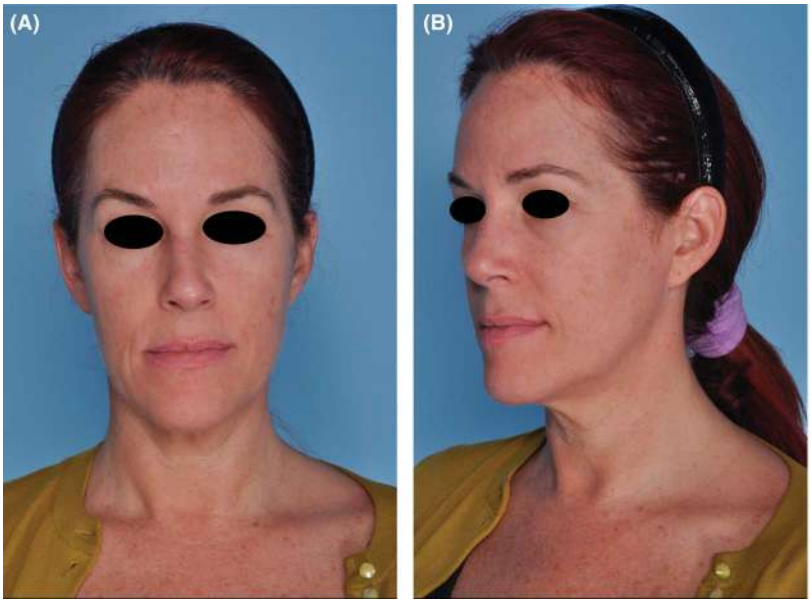

Figure 2. (A and B) The subject received an additional injection of onabotulinumtoxinA and treatment with Ca HA on the same day, approximately 1 year after treatment with MFU-V.

pulsed light (*n* = 1), MFU-V (*n* = 17), and incobotulinumtoxinA (*n* = 1).

During the 2-year study period, 29 subjects received a second dermal filler treatment with CPM HA (*n* = 25; 86%) or CaHA (*n* = 4, 14%) at the following areas: perioral (*n* = 20), periocular (*n* = 5), cheeks (*n* = 5), temples (*n* = 1), chin (*n* = 3), nasolabial folds (*n* = 2), tear trough (*n* = 1), lips (*n* = 2), forehead (*n* = 2), and glabella (*n* = 2). Most subjects were injected in more than one area.

The volume of CPM HA dermal fillers injected during the second treatment ranged from 0.1 to 2.0 mL, with most subjects receiving 1.0 mL. The volume of CaHA injected was 1.5 mL (*n* = 3) or 0.5 mL (*n* = 1). Target areas for the second treatment of CaHA were intradermal (*n* = 22), subdermal (*n* = 18), and

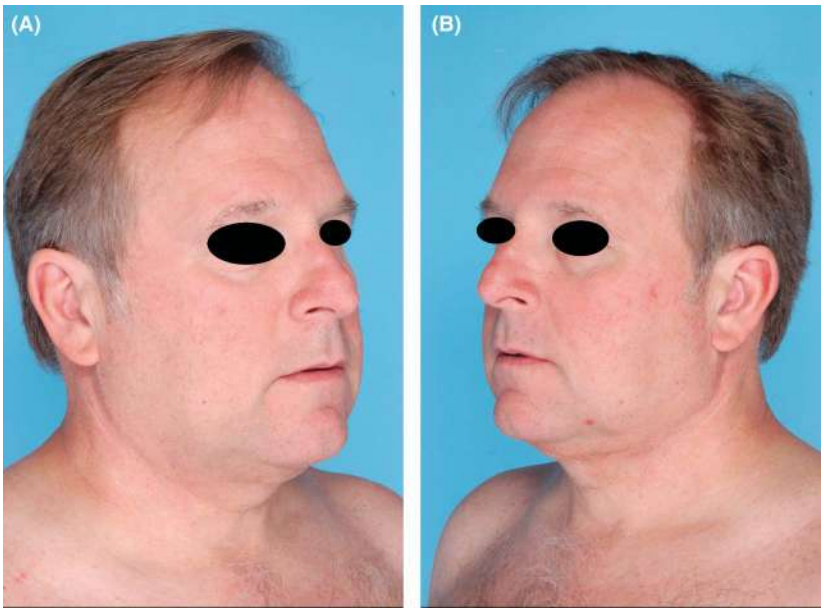

Figure 3. (A and B) This image was taken before full-face and neck treatment with MFU-V.

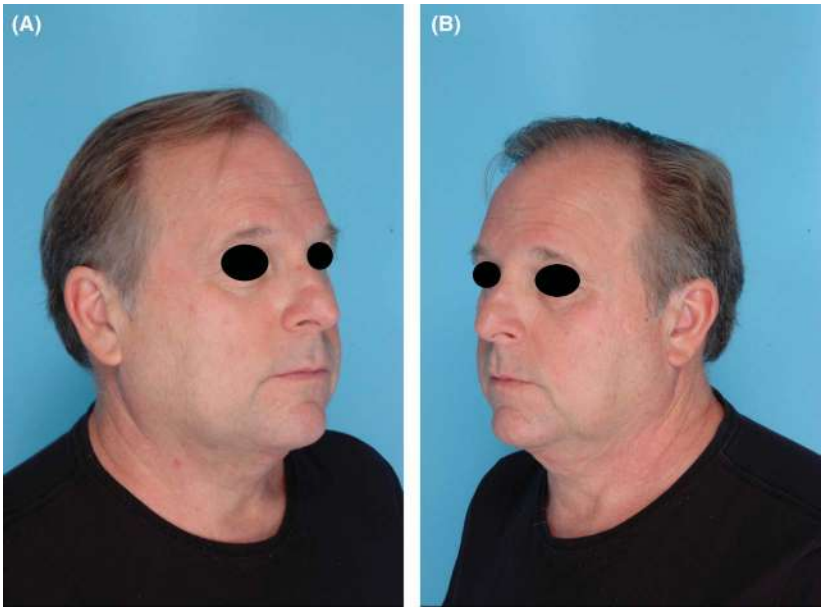

Figure 4. (A and B) The patient received incobotulinumtoxinA to the forehead, glabella, and periocular areas approximately 2 months later.

supraperiosteal tissues (*n* = 4). Additional treatments performed in 14 subjects at the same time as their CPM HA/CaHA treatment included onabotulinumtoxinA injections (*n* = 7), other dermal fillers (*n* = 5), abobotulinumtoxinA (*n* = 2), MFU-V (*n* = 2), and laser resurfacing (*n* = 1).

Ten subjects received a third treatment with CPM HA dermal filler (*n* = 9) or CaHA dermal fillers (*n* = 1) at the following areas: perioral (*n* = 8), periocular (*n* = 3), temples (*n* = 1), chin (*n* = 2), nasolabial folds (*n* = 1), hands (*n* = 1), jawline (*n* = 1), nose (*n* = 1), upper eyebrow (*n* = 1), forehead (*n* = 2), and glabella (*n* = 1). Most subjects were treated in more than one area. The volume of CPM HA dermal filler injected ranged from 0.1 to 1.0 mL, with most subjects receiving 1.0 mL. The volume of CaHA injected was 1.5 mL. The target tissue layers were intradermal (*n* = 13) and subdermal (*n* = 9). Additional treatments were performed in 6 subjects at the same time as their CPM HA or CaHA treatment: other dermal fillers (*n* = 4), onabotulinumtoxinA injections (*n* = 3), and laser resurfacing (*n* = 3).

Five subjects received a fourth CPM HA dermal filler treatment at the following areas: perioral (*n* = 5), periocular (*n* = 1), temples (*n* = 1), cheeks (*n* = 3), glabella (*n* = 1), and neck (*n* = 1). Most subjects had treatment in more than one area. The volume of injected product ranged from 0.1 to 1.0 mL, with most receiving 1.0 mL. Target areas were intradermal (*n* = 9) and subdermal tissues (*n* = 3). Additional treatments performed in 4 subjects at the same time as their CPM HA treatment included laser resurfacing (*n* = 2), another dermal filler (*n* = 1), and other brands of botulinum toxin A (BoNTA) injection (onabotulinumtoxinA, *n* = 3; abobotulinumtoxinA, *n* = 1).

Of the 20 subjects who received MFU-V and a CPM HA and/or CaHA dermal filler or incobotulinumtoxinA treatment on the same day, 9 received treatments in the same anatomical area (Table 3). Full-face MFU-V treatment was combined with 2 periocular treatments (CPM HA and CaHA), 3 cheek treatments (CPM HA), and 1 treatment of the temples (CaHA). Among all subjects, 59 (59%) also received other treatments, procedures, or multiple injections of the same product during the 2-year study period including various dermal fillers (*n* = 117), laser resurfacing (*n* = 12), radiofrequency treatment (*n* = 2), intense pulsed light (*n* = 1), light-emitting diode (*n* = 1) treatments, mesotherapy (*n* = 1), and other brands of BoNTA injection (onabotulinumtoxinA, *n* = 53; abobotulinumtoxinA, *n* = 4).

TABLE 3. Same-Day Combination Treatments

MFU-V–Treated Areas	*IncobotulinumtoxinA*	*CPM HA Filler*		*CaHA Filler*			
	Neck	*Periocular*	*Cheeks*	*Temple*	*Periocular*	*Perioral*	*Cheeks*
Neck	1						
Full face		1	3	1	1		
Perioral						1	
Cheeks							1

Adverse Events

Seven AEs were reported in 7 subjects (7%): bruising/purpura ($n = 4$), swelling ($n = 1$), paresthesia ($n = 1$), and herpes simplex virus (HSV) outbreak ($n = 1$). All were mild in severity, with the exception of 1 bruising event of moderate severity. One event of paresthesia and 2 bruising events were considered related to MFU-V treatment, and 1 event of swelling and 2 events of bruising were considered related to CPM HA or CaHA. The HSV outbreak was considered related to a combination of MFU-V, CPM HA, other hyaluronic acid (HA) fillers, and onabotulinumtoxinA. The HSV outbreak was treated with valcyclovir 1,000 mg twice daily for 2 days. Two events of swelling and bruising were treated with ice packs, 2 bruising events were treated with laser therapy, and 1 bruising event was treated with a combination of ice pack, arnica cream, and laser therapy. Four AEs resolved without sequelae and the outcome for the other 3 was unknown due to lack of follow-up. The moderate bruising event resolved in 26 days, and the paresthesia event resolved in 118 days. There were no serious AEs. Details of reported AEs are summarized in Table 4. Only 1 of the 9 subjects treated with MFU-V and a second aesthetic product on the same day experienced an AE: the subject who received both MFU-V and CaHA treatment to the cheeks experienced swelling at the filler injection site.

Discussion

After the introduction of BoNTA injections for the treatment of facial rhytides approximately 20 years ago,[15,16] there has been an increase in the number of available botulinum toxins, the development of a broad range of dermal fillers, and the introduction of numerous devices employing different types of energy to achieve facial rejuvenation. BoNTA injections and CaHA and HA fillers have been the subject of numerous clinical trials for aesthetic uses and have demonstrated favorable safety profiles.[17–21] The published literature also includes several randomized, prospective studies[8,22–24] and clinical experience[13,25] reporting the safety of combining toxins with dermal fillers as well as

TABLE 4. Adverse Events

Adverse Event	*Severity*	*Related Treatment*	*Intervention*	*Outcome*
HSV outbreak	Mild	MFU-V, CPM HA, other HA filler, onabotulinumtoxinA	Valcyclovir 1,000 mg BID × 2 d	Unknown
Bruising/purpura	Mild	CaHA	Pulsed dye laser	Unknown
Bruising/purpura	Mild	CPM HA	Pulsed dye laser	Unknown
Bruising/purpura	Moderate	MFU-V	Ice pack	Recovered
Paresthesia	Mild	MFU-V	—	Recovered
Bruising/purpura	Mild	MFU-V	Ice pack, topical arnica cream, pulsed dye laser	Recovered
Swelling	Mild	CaHA	Ice pack	Recovered

BID, twice daily.

toxins with intense pulsed light,[26] broadband light,[27] and radiofrequency.[28]

MFU-V uses intense focused ultrasound for precise microcoagulation of subcutaneous tissues[29,30] leading to an initial contraction and denaturation of collagen fibers; subsequent stimulation of de novo collagen synthesis and normalization of elastin fibers results in skin tightening.[31,32] To date, limited data are available concerning the combined use of MFU-V with other aesthetic treatments. One retrospective study assessed the combined use of MFU-V and ablative fractionated laser resurfacing to improve skin laxity and rhytides on the face and neck.[33] The results of this study indicated that combined therapy resulted in significantly improved skin laxity and photodamaged skin, because of theoretical synergy. The combined treatments also had a safety profile similar to the individual treatments, demonstrating that these 2 techniques can be safely administered together. Another retrospective study assessed the combined use of MFU-V with intense pulsed light and a poly-L-lactic acid dermal filler for facial rejuvenation.[5] The results of this study indicated that all 3 procedures may be safely performed in a single treatment session to multiple tissue planes with no change in overall safety profile when compared with each procedure being performed alone. These authors also speculated that synergistic effects may result from combining collagen-stimulating injectable products with the collagen-stimulating, energy-based device.

The present study was sponsored by the manufacturer of the MFU-V device to assess its safety when used together with its portfolio of injectable aesthetic products. All 101 subjects received treatment with MFU-V. Within 60 days of MFU-V treatment, 81 (81%) received CPM HA or CaHA, 18 (18%) received only incobotulinumtoxinA, and 2 subjects (2%) received CPM HA, CaHA, and incobotulinumtoxinA. A total of 59 (59%) subjects received other aesthetic treatments and procedures in addition to MFU-V, CPM HA, CaHA, and incobotulinumtoxinA. As 83% of subjects also received a filler within 60 days of MFU-V treatment, this supports the fact that when treating a population with a mean age of 55.3 years, multiple factors account for the ptotic brow, jowling, and neck laxity that prompts patients to seek skin tightening/lifting procedures. These factors include bone resorption, facial fat repositioning, and a decrease in collagen and elastin fiber fragmentation. As MFU-V is only able to address the changes in collagen and elastin, fillers are frequently needed to comprehensively address all concerns of the patients. Interestingly, only 74% of patients (n = 74) who were administered MFU-V also received treatment with toxin (onabotulinumtoxinA, n = 53; incobotulinumtoxinA, n = 17; abobotulinumtoxinA, n = 1). The authors speculate that the lower number of patients preferring neuromodulator treatment may be due to the type of patient who present for strictly skin laxity and their preference for noninvasive energy-based treatments. It is perhaps with the educational insight of the physician that explains that the ptotic changes seen are also due to volume loss, requiring a combined approach using MFU-V with injectable treatments to more effectively address their concerns.

A relatively small number of reported AEs (n = 7) were associated with combined use of dermal filler products and/or incobotulinumtoxinA within 60 days of MFU-V, suggesting that MFU-V may be safely performed after the use of incobotulinumtoxinA and dermal fillers and that injectable products may be safety used after MFU-V. All AEs were of mild or moderate severity and only 1 episode of HSV outbreak was considered related to the combined treatments. No safety signals were apparent that suggested any risk associated with the combined use of MFU-V with incobotulinumtoxinA or dermal fillers. The authors believe the benefit of synergistic effects far outweigh the risk of combining these treatment modalities because there were few AEs observed as previously reported by others after the combined use of incobotulinumtoxinA and dermal fillers.[8,13,22–25]

Although limited by the relatively small number of treated subjects and the retrospective study design, the results of the present chart review suggest the combined use of MFU-V with other CPM HA and CaHA dermal fillers seems to share similar safety profiles to individual treatments.

Conclusion

The results of this retrospective review demonstrate the safety of MFU-V when combined with incobotulinumtoxinA injections, CPM HA, and CaHA dermal fillers.

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Address correspondence and reprint requests to: Sabrina G. Fabi, MD, Goldman, Butterwick, Fitzpatrick, Groff and Fabi Dermatology Cosmetic Laser, 9339 Genesee Avenue, Suite 300, San Diego, CA 92121, or e-mail: SFabi@gbkderm.com