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Early Experience in 100 Consecutive Patients With Injection Adipocytolysis for Neck Contouring With ATX-101 (Deoxycholic Acid)

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BACKGROUND Deoxycholic acid (DCA) is approved for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat.

OBJECTIVE To assess early treatment experience with DCA injection in a clinical practice setting.

MATERIALS AND METHODS In this single-center, prospective, single-arm, observational study, 100 consecutive patients seeking to decrease submental fullness received subcutaneous DCA (2 mg/cm^2) injections in the submental area (maximum of 6 sessions at ≥1 month intervals). Treatment response was assessed 1 and 5 to 7 weeks posttreatment using the clinician-reported submental fat rating scale (CR-SMFRS) and retrospective independent photograph review by 2 physicians.

RESULTS Overall, 100 patients had 152 treatment sessions (58, 33, 8, and 1 patients had 1, 2, 3, and 4 sessions, respectively). CR-SMFRS score improved by ≥1 point from baseline in 88 (88%) patients; of these, 46, 33, 8, and 1 patients had 1, 2, 3, and 4 sessions, respectively. Local edema, numbness, and tenderness were reported for a mean (SD) of 7.7 (5.3), 28.5 (11.4), and 3.5 (3.5) days, respectively. Two patients experienced marginal mandibular nerve paresis.

CONCLUSION Deoxycholic acid injection, a minimally invasive procedure for neck contouring, was effective and generally well tolerated in the private practice setting.

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Facial aesthetic surgical procedures such as face and neck lifts consistently are among the top 5 cosmetic surgical procedures performed annually in the United States.[1–3] Among such procedures, neck contouring is gaining popularity, and various novel technologies (Ultherapy, Merz Aesthetics, Merz North America; CoolMini, ZELTIQ Aesthetics, Pleasanton, CA; Thermi, Almirall Company, S.A.) are available to target this anatomic region. Use of injections in cosmetic procedures also is increasing; nearly 10 million patients underwent treatment with botulinum toxin type A, dermal fillers, or both in 2015, which represents a 7% increase from 2014.[1–3] Consequently, interest in rejuvenation strategies for the lower third of the face has surged, and patients increasingly are seeking ways to reduce submental fullness.

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Submental fat accumulates in a distinct compartment within the preplatysmal fat[4] is considered aesthetically unappealing[5] and can have a negative psychological impact on patients.[6]

Accumulated fat deposits treated invasively with surgery liposuction etc., can be associated with serious complications and substantial recovery times[7,8]; evidence supporting effectiveness of noninvasive energy devices is also limited.[9]

Lipolytic injectables (injection lipolysis, mesotherapy, or lipodissolve) are minimally invasive, alternative approaches for reducing accumulated submental fat, wherein one or more compounds are injected into the submental fat.[10]

Among them deoxycholic acid (DCA), a naturally occurring bile acid, emulsifies fat for absorption in the intestine with nonselective cell-lysis ability[11] and acts by irreversibly disrupting the adipocyte membrane causing adipocytolysis.[12] DCA injection (ATX-101; KYBELLA [United States], BELKYRA [Canada]; KYTHERA Biopharmaceuticals, Inc., Westlake Village, CA, acquired by Allergan, Inc.) is a proprietary formulation of synthetically derived DCA that is FDA-approved for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat.[12–14]

The efficacy and safety of DCA injections in the submental fat area was demonstrated in 4 phase 3 randomized controlled trials (RCTs).[5,15–18] Assessing treatment experience in everyday clinical practice is warranted. DCA has a nonselective cell-lysis ability; however, affinity is lower in proteinaceous tissues versus fatty tissue. Therefore, adipose tissue is more susceptible to DCA versus surrounding tissue. RCTs are known to use stringent inclusion and exclusion criteria, and outcome-driven treatment protocols. To this end, a prospective, observational study was conducted using patients from private practice to assess real-world, early experience with initial treatment sessions of DCA injections for its approved indication. To the author's knowledge, this report is the first to describe experience with DCA injections for reducing submental fat in a clinical practice or academic institution setting in the United States since the product became available for use.

Methods

Study Design

This prospective, observational study carried out at LUXURGERY clinic (New York, NY) between June 2015 and February 2016 was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Tripartite Guidelines for Good Clinical Practice. Written informed consent was obtained from each patient.

Patients

One hundred consecutive patients between 18 and 80 years old, who were seeking improvement in convexity/fullness associated with submental fat, were enrolled. Patients were excluded if they had other potential causes of submental convexity or fullness (e.g., thyromegaly, cervical adenopathy, submandibular ptosis, and excessive skin laxity), infection at injection site, previous use of injectable lipolytic agent, were using anticoagulants, or were pregnant. Caution was exercised in patients with changes in anatomy or landmarks, or who had scar tissue that may have impacted the ability to safely administer DCA injections or obtain the desired aesthetic result.

Treatment

Deoxycholic acid (10 mg/mL) for subcutaneous injection is available as a sterile solution in a 2-mL clear, colorless vial for single-patient use. Vials were stored at 20 to 25°C (68 to 77°F), and excursions between 15 and 30°C (59 to 86°F) were permitted.

Procedure

Before treatment, perceived change in neck anatomy associated with submental fullness was assessed, and the preplatysmal fat within the treatment area was identified (Figure 1A). Thereafter, the treatment area was marked with a surgical pen, and a 1-cm injection grid was applied to mark the injection sites (Figure 1B). The needle (32 gauge) was placed with respect to the

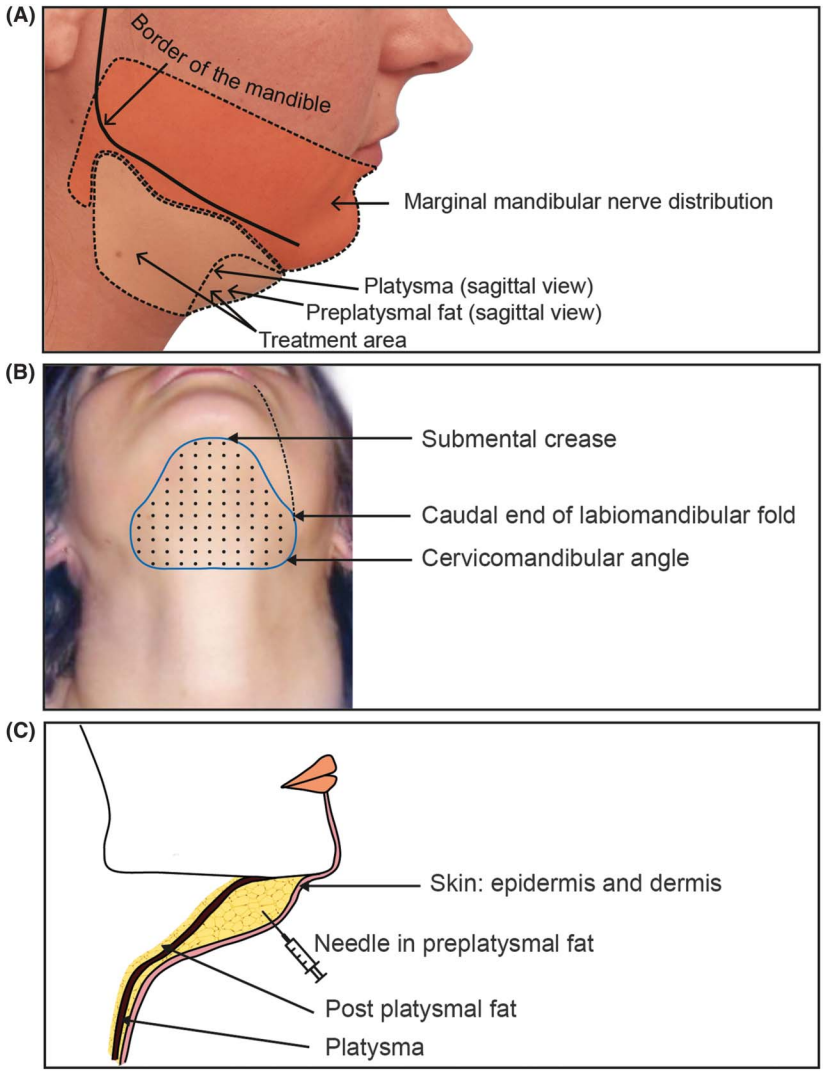

Figure 1. (A) Landmarks/identification of area of submental fat distribution; (B) Injection pattern; (C) Location of needle in the preplatysmal fat.

mandible to avoid injury to the marginal mandibular nerve (MMN; motor branch of the facial nerve) allowing DCA to be injected within the target submental fat treatment area only (Figure 1C). Deoxycholic acid was injected subcutaneously in the submental fat area using an area-adjusted dose of 2 mg/cm^2. Dose was not tapered laterally. A single-treatment session comprised a maximum of 75 injections: 0.2 mL per injection (maximum, 15 mL), spaced 1 cm apart. Based on results from RCTs,[5,15–18] patients could undergo a maximum of 6 single-treatment sessions at least 1 month apart. Ice packs, oral analgesia, topical local anesthetic, and injectable local anesthetic were used before and after treatment as needed. Number of injections per session and number of sessions depended on the patient's submental fat distribution. The aesthetically ideal treatment goal, which was based on each patient's anatomy and overall expectations, was explained to each patient before beginning treatment.

Efficacy Assessments

Treatment response was evaluated using the clinician-reported submental fat rating scale (CR-SMFRS—used with permission from Allergan plc)[15,17] which was measured for each treatment session at baseline, Week 1 posttreatment, and between Weeks 5 and 7 posttreatment. Using the CR-SMFRS, submental convexity was evaluated by the clinician on a 5-point

ordinal scale (0 = absent; 1 = mild; 2 = moderate; 3 = severe; and 4 = extreme).[15,17] Overall treatment response was confirmed by retrospective independent review of photographs by 2 physicians in the practice of plastic surgery who were blinded to the patients' treatment status. Photographs were taken at each follow-up visit.

Safety Assessments

Patients were evaluated for injection-site adverse events (AEs) and other AEs at each follow-up visit. Patients reported AEs by telephone or visit to the clinic when required.

Statistical Analyses

A cross-sectional evaluation of data was performed, and categorical and continuous variables were summarized. Incidence was calculated as the ratio of event count divided by total event count. Because of high dispersion of continuous variables, comparisons were performed using the Mann–Whitney *U* test. Categorical variables were compared using chi-square/Fisher exact test/Kruskal–Wallis test. Data were compared between patients receiving single versus multiple (≥2) treatment sessions (IBM SPSS Statistics version 21.0).

Results

Patient Demographics and Baseline Characteristics

Overall 100 patients were treated: 39 men and 61 women (Table 1). Mean [SD; min, max] patient age was 45.4 [12.2; 23, 76] years. Mean body mass index (BMI) was 26.1 (4.4; 17.3, 44.8) kg/m^2, and 57 patients had a BMI ≥25 kg/m^2. Seventeen patients had a Fitzpatrick score of >3. Most patients had a baseline CR-SMFRS score of 1 or 2 (19 and 34, respectively). Among 43 patients with a previous plastic surgery procedure, the most common (7 [16.3%]) was neck liposuction. More men than women (66.7% [27/39] vs 50.8% [31/61]) had no history of cosmetic procedures; of these, more men than women (18.5% [5/27] vs 12.9% [4/31]) returned within 6 months for cosmetic procedures other than neck contouring. No statistical differences in age, sex, BMI, BMI <25 and ≥25 kg/m^2, or history of previous cosmetic procedures were detected between single- and multiple-treatment session groups.

Procedural Outcomes

Overall, 100 patients had a total of 152 (58: single; 42: multiple [a total of 94]) treatment sessions. In the multiple–treatment-session group, most (33/42; 78.6%) patients had 2 sessions; 8 (19.0%) had 3 sessions, and 1 had 4 (2.4%) sessions. The patient follow-up duration between treatments varied from 24 to 172 days.

Overall, patients were administered a mean (SD) of 6.7 (2.3) mL of DCA per session, and more DCA was administered per session in the multiple-than single-treatment session group (7.0 [2.4] vs 6.2 [2.2] mL, respectively; $p = .026$). Among patients with multiple-treatment sessions, mean (SD) time from previous injection to second, third, and fourth treatments was 47.9 (27.9), 63.3 (20.8), and 42.0 (–) days, respectively.

Patients were administered a mean (SD) of 5.9 (2.0) mL local anesthetic per session, with more administered to patients in the multiple- than single-treatment session group (6.2 [2.1] vs 5.4 [1.8] mL, respectively; $p = .022$). No significant difference was observed between treatment groups in use of ice packs (single: 57/58 [98.3%]; multiple: 91/94 [96.8%]) or pre-injection oral analgesia (single: 55/58 [94.8%]; multiple: 85/94 [90.4%]).

Treatment Response

CR-SMFRS score improved by ≥1 point from baseline in 88 (88%) patients; of these, 46, 33, 8, and 1 patients had 1, 2, 3, and 4 treatment sessions, respectively. Based on CR-SMFRS results, 12/58 patients did not respond to a single treatment; however, 46 patients had an improvement of ≥1 point (45 [45%] by 1 point and 1 [1%] by 2 points). In contrast, all 42 patients who underwent multiple-treatment sessions responded to treatment (31 [31%] by 1 point and 11 [11%] by 2 points). Examples are shown in Figure 2 and

TABLE 1. Patient Demographics and Baseline Characteristics

	1 Treatment Session	*≥2 Treatment Sessions*	*Total*	*p* (Chi-square)
n	58	42	100	—
Treatment sessions				
2	—	33	—	—
3	—	8	—	—
4	—	1	—	—
Age, mean (SD), yr	46.3 (12.2)	44.3 (12.1)	45.4 (12.2)	.455*
Sex, n (%)				
Man	18 (31)	21 (50)	39 (39)	.055
Woman	40 (69)	21 (50)	61 (61)	
BMI, mean (SD), kg/m^2	25.8 (4.6)	26.6 (3.9)	26.1 (4.4)	.295*
<25	26 (44.8)	17 (40.5)	43 (43.0)	.664
≥25	32 (55.2)	25 (59.5)	57 (57.0)	
Fitzpatrick score				
≤3	52 (89.7)	31 (73.8)	83 (83.0)	.037
>3	6 (10.3)	11 (26.2)	17 (17.0)	
Previous plastic surgery procedure, n (%)				
Yes	23 (39.7)	20 (47.6)	43 (43.0)	.427
No	35 (60.3)	22 (52.4)	57 (57.0)	
Previous procedure, n				
Blepharoplasty	0	1	1	
Breast augmentation, blepharoplasty	1	0	1	
Breast reduction	0	1	1	
Breast reduction, liposuction, tummy tuck	1	0	1	
Bilateral sagittal split osteotomy	0	1	1	
Coolsculpt	0	1	1	
Face laser	2	0	2	
Facelift/neck	1	0	1	
Facelift/neck, brow, neck liposuction	1	0	1	
Facelift/neck, chin implant, tummy tuck	1	0	1	
Hair transplant	0	1	1	
Injectable	4	1	5	
Injectable, blepharoplasty	0	1	1	
Injectable, facial surgery	1	0	1	
Injectable, liposuction	0	2	2	
Injectable, rhinoplasty	0	1	1	
Liposuction	3	2	5	
Liposuction, rhinoplasty	1	1	2	
Lower body lift	1	0	1	
Miniface, tummy tuck, liposuction, aug/pexy	1	0	1	
Neck liposuction	3	3	6	
Necklift, breast reduction	1	0	1	
Rhinoplasty	0	3	3	
Rhinoplasty, blepharoplasty	1	0	1	

*Mann–Whitney *U*.

BMI, body mass index; SD, standard deviation.

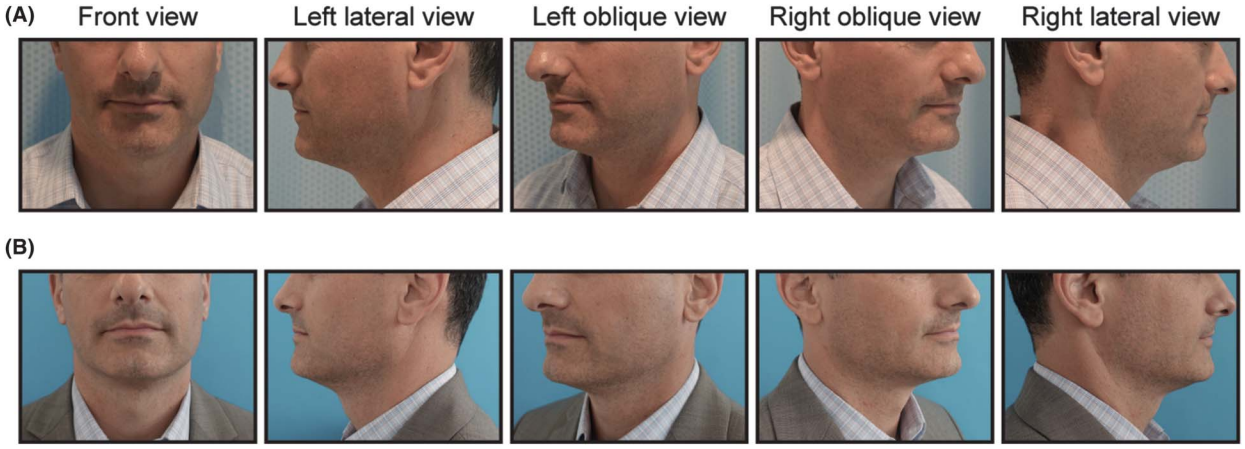

Figure 2. Photographs showing response for a 45-year-old male patient who underwent 2 treatment sessions (9 mL deoxycholic acid total for all sessions; 11 weeks apart); (A) before treatment, (B) 20 weeks after second session.

Supplemental Digital Content 1, Figure, http://links.lww.com/DSS/A71.

Safety Outcomes

In the single-treatment session group, nausea, vomiting, and headache were reported in 1 patient each (Table 2). Overall, local edema, numbness, and tender injection sites were reported for a mean (SD) of 7.7 (5.3) days, 28.5 (11.4) days, and 3.5 (3.5) days, respectively. Patients who underwent multiple-treatment sessions experienced edema significantly longer than those who had a single session (mean [SD] duration: 2 sessions, 6.3 [5.2] days and 3 sessions, 3.7

TABLE 2. Adverse Events

	1 Treatment Session	*≥2 Treatment Sessions*	*Total*	*p* (Fisher's Exact Test)
n	58	42	100	
Treatment sessions	58	94	152	
Nausea	1	0	1	1.000
Vomiting	1	0	1	1.000
Headache	1	0	1	1.000
Alopecia	3	5	8	.275
Local edema (days postsession), mean (SD)	8.6 (5.3)*	5.8 (4.8)†	7.7 (5.3)	.0001‡
Local numbness (days postsession), mean (SD)	28.4 (11.6)§	28.6 (11.4)‖	28.5 (11.4)	.608‡
Local tenderness (days postsession), mean (SD)	3.1 (3.3)¶	3.7 (3.6)#	3.5 (3.5)	.356‡
Paresis, *n* (days postsession for resolution)	2 (17, 22)	0	2	.226‡
Bruising, *n*	10	13	23	.538**

*$n = 55$.
†$n = 88$.
‡Mann–Whitney *U*.
§$n = 53$.
‖$n = 84$.
¶$n = 56$.
#$n = 93$.
**Chi-square.
SD, standard deviation.

[1.6] days vs 1 session, 8.6 [5.3] days; $p < .0001$, Kruskal–Wallis test). However, no significant difference was noted between treatment groups in duration of numbness or tender injection sites. Duration of local edema, numbness, and tender injection sites did not differ significantly between men and women (7.1 [4.5] vs 8.1 [5.8] days; 30.6 [13.2] vs 26.4 [9] days; and 3.3 [3.3] vs 3.5 [3.7], respectively). No hyperpigmentation was observed among patients with Fitzpatrick score >3.

MMN paresis was reported in 2 patients in the single-treatment session group, with recovery times of 17 and 22 days. Postinjection bruising was reported after 23 of 152 sessions, with no significant difference between multiple- and single-treatment session groups (13/94 [13.8%] vs 10/58 [17.2%]; $p = .538$), and transient alopecia at injection site was noted in 8 of 39 male patients; 5 of 21 [23.8%] who underwent multiple sessions versus 3 of 18 [16.7%] who underwent single session ($p = .702$) (Table 2).

Discussion

The focus of this study was to assess real-world, early experience with procedural and treatment outcomes after administration of DCA injections for treatment of accumulated submental fat, including durations of swelling, numbness, tenderness, and alopecia. Most patients (88/100) showed improvement of ≥1 point on the CR-SMFRS, which was considered clinically meaningful in the pivotal RCTs.[15,17] Of these, 46 patients underwent only 1 treatment session to achieve this improvement. Both single- and multiple-treatment sessions were generally well tolerated.

In the pivotal RCTs, patients underwent up to 6 treatment sessions.[5,15–18] In Refine-1, 64.1% (164/256) of patients required the maximum permissible 6 treatment sessions to achieve protocol-defined response. Patients who underwent fewer than 6 treatment sessions did so because of insufficient submental fat for further treatment, dissatisfaction, or AEs.[16] In other RCTs, approximately 80% of patients completed the 4 planned treatment sessions.[15,17] In contrast, in the present study, 58, 33, 8, and 1 patients underwent 1, 2, 3, and 4 sessions, respectively. Several factors (e.g., time-delimited nature of the analysis, early patient satisfaction or dissatisfaction, patient willingness to undergo multiple-treatment sessions, AEs, lack of patient enthusiasm to pursue the ideal aesthetic goal, and costs) might have contributed to the low number of treatment sessions. Nevertheless, 42 of the 100 patients returned for a second treatment session, suggesting any side effects were tolerable, manageable, or both. Furthermore, several patients mentioned improvement after a single-treatment session and expressed initial satisfaction with the treatment results. Patients possibly underwent all planned treatment sessions in earlier studies, despite seeing significant and satisfactory changes at lower number of treatments, because of no financial burden. In addition, if the treatment periods were to be extended, more patients would return for subsequent treatments at their convenience. This is also reflected in RCTs reporting discontinuation rates of ∼7% to 11%.[17,18] Further, we noted that the patient follow-up duration between treatments varied from 42 to 172 days compared with ∼28 days reported in RCTs.[5,15–18]

Many patients (57/100) in this study had no previous cosmetic procedures, challenging popular beliefs regarding body dysmorphic disorder.[19,20] Compared with the pivotal RCTs, more men (39% vs 16.8%–28.0%[5,15–18]) were interested in this cosmetic procedure. Furthermore, only one third of the men, compared with half the women, had a history of previous cosmetic procedures. Moreover, the proportion of procedure-naïve men who returned within 6 months for additional cosmetic procedures also was higher among men (19% [5/26]) than women (12.9% [4/31]). These observations indicate procedure-naïve individuals are likely to come back for other cosmetic procedures, suggesting that DCA injections for neck fullness could serve as a practice-building tool.

When comparing results from this study to those from the pivotal RCTs,[5,15–18] the total amount of DCA administered in this study was substantially lower than that administered in the RCTs (mean [SD]: 6.7 [2.3] mL vs 25.0 [13.4] mL[16]; approximately17.0 [7.9] mL for 1-mg/cm^2 dose; approximately15.0 [8.2] mL for 2-mg/cm^2 dose).[15,17] A higher volume may have

been required in the RCTs because patients had moderate to severe submental fat, which required more treatment sessions.[15–17] Further, injection volume per session decreased as session number increased (from 6.2 [2.1] to 4.3 [2.2] mL) in Refine-1.[16] In contrast, in this study, the volume of DCA injected per session increased as session number increased; use of local anesthetic also increased significantly. Potential reasons for this observation include time to become proficient with the procedure and making judgment calls in the subsequent session with regard to the change in submental fat for the volume of DCA administered. Nevertheless, the treatment response for doses of DCA suggests that the approach was conservative in this study, and comparisons with RCTs should be made with caution given differences in procedure, submental fat severity, and outcome measures.

AEs reported in the current study were fewer, yet similar to those reported in RCTs; most were injection related. Local edema, numbness, and tenderness occurred in 100% of patients. In comparison, local edema and numbness were reported in 50% to 65% of patients in RCTs, possibly because of fewer injections per session. Based on results of the present study, patients undergoing this procedure should expect local edema, numbness, and tenderness to last for slightly longer than 1 week, approximately 4 weeks, and approximately 3 to 4 days, respectively, with no substantial difference between men and women. The duration of edema is likely to decrease with subsequent treatment sessions.

Mild transient alopecia at the injection site was seen in 8 of 39 men, compared with none in the pivotal RCTs.[15–17] The alopecia was monitored between treatment sessions and all cases resolved within 6 weeks of the last treatment session. Postinjection bruising occurred in fewer patients (20%) in this study than in RCTs (50%–60%).[15–17] Cases of induration and fibrosis were not observed in this study but were in approximately 20% of patients in RCTs, possibly because of the higher number of injections per session for the total dose administered in this study. No patient with a Fitzpatrick score >3 in the current study presented with hyperpigmentation.

The incidence of MMN paresis was low in both the RCTs (2%–4%)[15–17] and in the present study (2/100 [2%]). Two cases of MMN paresis occurred in the patients purposefully treated close to the jowl. Both patients were injected slightly more superior and within the zone of distal arborization of the MMNs intended, injections were into the subcutaneous plane. Interestingly, both patients manifested with unilateral MMN paresis. One would expect that the patients would have signs consistent with bilateral paresis, since equal doses of DCA were injected into the similar subcutaneous plane bilaterally. One could hypothesize that normal anatomic variants exist, and at the level of the jowl, significant branching of the MMN might have existed in these patients.

Limitations of this study include a restricted patient population (i.e., single, private practice), lack of control group, assessment of patient willingness to pursue the ideal aesthetic goal, and a stringent follow-up. However, these limitations represent real-world scenarios in aesthetic surgery private practice. Also, in contrast to the clinical trial setting, where an aesthetically ideal treatment response is aggressively defined and pursued, the treatment response in the real-world is likely to be influenced by surgeon's apprehensions, variable patient satisfaction, and cost. Furthermore, my early experience could not support the physicians CR-SMFRS score with the patient satisfaction score which should have improved with increasing number of treatment sessions.

Collectively, the results suggest that an initial treatment response with use of low-dose DCA followed by close and routine patient follow-up is important for managing AEs and further patient expectations. The initial apprehension reflecting in the use of low-dose DCA is likely to determine the strategy for the next treatment session inclusive of patient expectation. Patient follow-up is likely to vary; patients might postpone the next treatment session for or prefer to undergo this procedure during winter months when clothing can hide transient redness and swelling. Distributing the dose and volume of DCA over a greater number of injections per session and avoiding injection of DCA into the skin may reduce skin-related AEs and make the procedure more acceptable to patients.

The time limited nature of the analysis led to patients treated only once who came back later on after the cutoff date. Basically, of the single-treatment patients, many opted for subsequent treatments but have the flexibility to come for a repeat procedure as and when convenient since there is no fixed interval as to when a patient must be treated again. Patients are encouraged to undergo at least 2 treatments to see a satisfactory change, but a change in CR-SMFRS scores may be significant with just one treatment. In addition, studies are needed to evaluate the dosing, efficacy, and safety of DCA injection for reducing unwanted fat in other areas of the body.

Conclusion

DCA injection is a safe, well tolerated, and minimally invasive alternative for permanent submental fat reduction. Patients are likely to require >1 session to achieve the desired aesthetic goal from a clinicians' perspective; however, an improvement in CR-SMFRS score, was seen in many patients after a single treatment. The number of additional treatment sessions will be influenced by numerous factors including consensus between physician and patient, treatment response, physician's judgment, and patient satisfaction. When compared with RCTs, DCA injection volume and number of sessions needed to reach aesthetic goals are likely to be less in private practice. In my private practice, I used less volume of DCA and a higher number of injections than in the RCTs but was able to provide satisfactory results in most patients. Caution during needle placement is essential because of the nonselective lytic nature of DCA, the effects of which are dose related.

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