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Novel Expanded Safe Zone for Reduction of Submental Fullness with ATX-101 Injection

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Background: ATX-101 (deoxycholic acid injection; Kybella) provides an approved nonsurgical treatment option for reduction of submental fullness caused by submental fat. Current one-size-fits-all recommendations for the use of ATX-101 limit treatment to a central area, which may not provide complete resolution of submental fat for some patients. An expanded safe zone is described, allowing for individualized, comprehensive treatment of submental fat with ATX-101 according to each patient's anatomy and desired outcomes.

Methods: A retrospective review was conducted of patients treated with ATX-101 for excess submental fat between June of 2015 and December of 2016 at a single plastic surgery practice. The expanded safe zone was developed to isolate the distinct fat compartments of the submental area and includes a no-treatment zone to avoid the marginal mandibular nerve. The extent of ATX-101 treatment required in each zone was determined by assessment of subcutaneous adipose tissue. A 1-cm grid was used to mark the treatment area before injection of ATX-101 (2 mg/cm^2). Improvement (defined as decreased palpable and/or visible submental fullness) was determined at least 4 months after the final treatment. Adverse events were recorded at each visit and reported by patients by means of telephone.

Results: Overall, 167 patients were included in this analysis. Improvement in submental fullness was achieved in 160 of 167 patients (95.8 percent). The majority of adverse events consisted of temporary injection-site edema, numbness, and tenderness.

Conclusion: An understanding of submental anatomy and careful assessment of each patient's submental fat allows for individualized treatment with ATX-101 beyond the central region of the neck without increased risk of adverse events. (*Plast. Reconstr. Surg.* 144: 995e, 2019.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, IV.

Approval of ATX-101 [deoxycholic acid injection; Kybella in the United States; Belkyra in Canada, Australia, Europe, and South Korea; Kythera Biopharmaceuticals, Inc., an affiliate of Allergan (Allergan plc, Dublin, Ireland)] for reduction of submental fullness because of submental fat[1,2] has led to widespread interest in using this medication as an alternative to liposuction in the area under the chin. Standard markings

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according to the ATX-101 package insert provide for treatment of only a small central area of submental fullness (Fig. 1).[1] This treatment zone is bordered superiorly by the submental crease, laterally by inferior extension of the oral commissures, and inferiorly by the thyroid notch. This one-size-fits-all approach undertreats patients who have fuller necks, especially those with adipose deposition outside the central region.

Cadaveric dye studies have demonstrated that discrete submental fat compartments reside within the preplatysmal fat.[3,4] These compartments are bounded superiorly by the submental ligaments and platysma-mandibular ligaments, laterally by the paramedian platysma-retaining ligaments, dorsally by the submandibular platysma-retaining ligaments, and inferiorly by the hyoid (true) ligament. Knowledge of these submental fat compartments provides an anatomical basis for patient-customized treatment with ATX-101.

Adverse events associated with ATX-101 are often localized to the injection site and transient, and include edema, numbness, tenderness, and bruising, along with marginal mandibular nerve paresis. The incidence of temporary marginal mandibular nerve paresis reported in the phase 3 randomized controlled trials conducted in the United States and Canada following ATX-101 injection in the central region (4.3 percent)[5–7] is similar to the incidence reported after liposuction or cervical rhytidectomy (1 to 5 percent).[8–10] Cadaveric studies have shown the marginal mandibular nerve to be less than 4.5 cm anterior to the gonion and less than 2 cm below the inferior border of the mandible.[11] Therefore, it is recommended that ATX-101 injections should be avoided in the area 1.0 to 1.5 cm below the inferior mandible from the gonion to menton.[1]

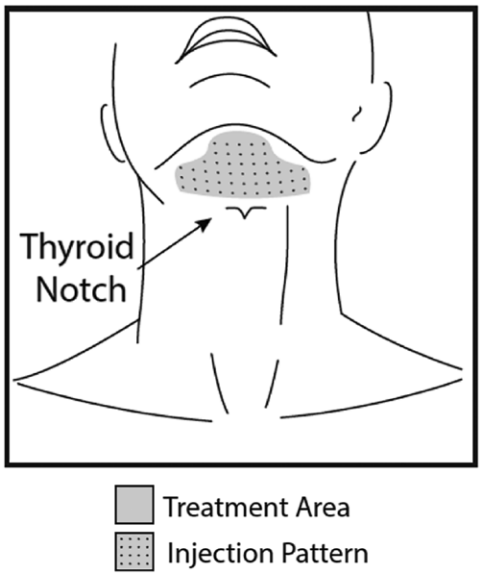

Fig. 1. Recommended ATX-101 treatment area and injection pattern based on the package insert. [Kythera Biopharmaceuticals, Inc. Kybella (deoxycholic acid) injection (prescribing information). Westlake Village, Calif: Kythera Biopharmaceuticals, Inc; 2015. Available at: https://www.allergan.com/assets/pdf/kybella_pi. Accessed March 1, 2018.] ©Allergan.

With an understanding of submental fat anatomy and potential adverse events, an expanded safe zone was developed for patient-customized treatment of submental fat with ATX-101. The purpose of the current analysis was to evaluate the safety and efficacy of treating patients with excess submental fat using the expanded safe zone.

PATIENTS AND METHODS

Study Design and Patient Selection

This was a retrospective review of patient data collected between June of 2015 and December of 2016. All patients were treated with ATX-101 for excess submental fat at a plastic surgery practice (LUXURGERY, New York, N.Y.) by a single clinician (S.M.S.). Written informed consent was obtained from each patient.

Patients aged 18 to 80 years seeking improvement in the appearance of submental convexity/fullness associated with submental fat were eligible for ATX-101 treatment. Patients were excluded if they had other potential causes of submental convexity/fullness (e.g., thyromegaly, cervical adenopathy, submandibular ptosis, or excessive skin laxity), infection in the treatment area, history of use of an injectable lipolytic agent, use of anticoagulants, or pregnancy. Patients may have been ineligible if they presented with anatomy/landmarks or presence of scar tissue that could impact the ability to safely inject ATX-101 or obtain the desired aesthetic result.

Expanded Safe Zone

Based on insights from anatomical studies of submental fat compartments,[3,4] a novel expanded safe zone was designed denoting topographic regions correlated to distinct fat compartments (Fig. 2). A no-treatment zone to avoid the marginal mandibular nerve is defined by the area 2.0 cm inferior to the mandible. The recommended

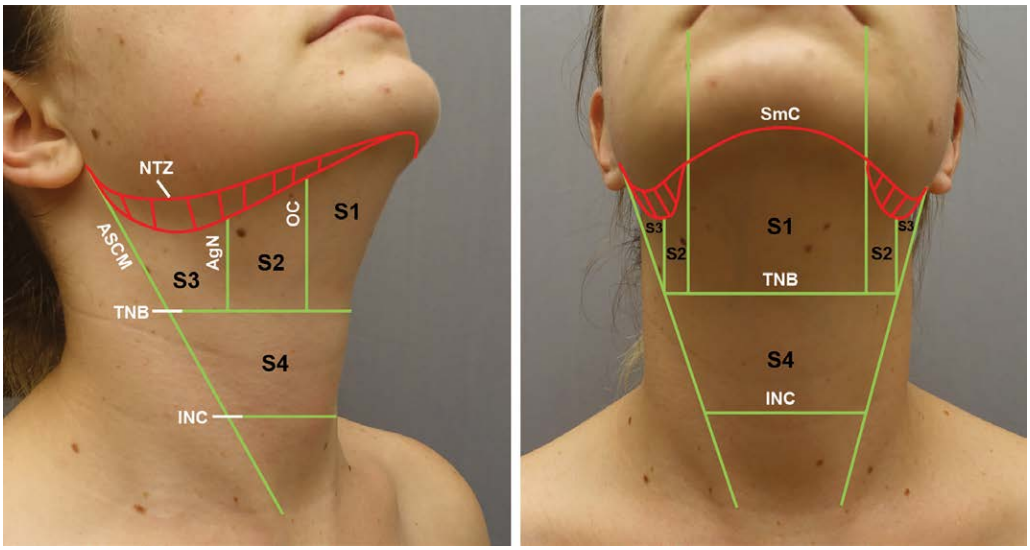

Fig. 2. Submental safe zones for ATX-101 treatment. Potential treatment zones are marked as S1, S2, S3, and S4. Zone borders are defined by the submental crease (*SmC*), thyroid notch border (*TNB*), inferior neck crease (*INC*), inferior extension of the oral commissures (*OC*), inferior extension of the antegonial notch (*AgN*), anterior border of the sternocleidomastoid muscle (*ASCM*), and inferior border of the no-treatment zone (*NTZ*) (*red hatched area*).

treatment area according to the ATX-101 package insert is referred to as zone S1. Table 1 details the anatomical borders of each treatment zone in the expanded safe zone.

Treatment Procedure

Before treatment, the submental area was marked with expanded safe zone boundaries, and submental fullness in each of the six zones of the expanded safe zone was assessed visually and through palpation by the clinician. The 1-cm injection grid provided with the ATX-101 package was applied to the treatment area, avoiding the region of the marginal mandibular nerve. ATX-101 (2 mg/cm^2) was administered in 0.2-ml injections next to the grid markings and perpendicular to the surface at a depth of 6 to 10 mm using a 0.5-inch, 32-gauge needle. Patient comfort measures included local anesthesia (lidocaine plus epinephrine 10 minutes before treatment), postinjection ice (for 48 hours after treatment), and postinjection analgesia (acetaminophen).

The use of expanded safe zone treatment, the volume of ATX-101 injected, and the total number of ATX-101 treatments were tailored to the individual patient's submental fat distribution and treatment goals. Patients did not necessarily receive ATX-101 injections in all six zones of the expanded safe zone at every session. Rather, expanded safe zone treatment was used in all zones with excess submental fat with the goal of treating to endpoint. Often, lateral submental fat would resolve first (because of less fat density in this region); therefore, subsequent treatments would focused on zone S1. According to the package insert, patients could receive up to six ATX-101 treatments with a maximum of 10 ml per session.[1] Patients were counseled that the typical number of treatments ranges from two to four, with approximately 6 weeks between sessions. During each follow-up visit, visual and palpation

Table 1. Borders of the Various Expanded Safe Zones for Injection of ATX-101

	Borders		
Zone	**Superior**	**Inferior**	**Lateral**
S1	Submental crease	Thyroid notch border	Inferior extensions of oral commissures
S2	2.0 cm below inferior border of mandible	Thyroid notch border	Inferior extensions of oral commissure and antegonial notch
S3	2.0 cm below inferior border of mandible	Thyroid notch border	Inferior extension of antegonial notch and anterior border of sternocleidomastoid muscle
S4	Thyroid notch border	Inferior neck crease	Anterior borders of sternocleidomastoid muscle

assessment of remaining submental adiposity were used to decide whether further treatment was warranted. The interval between treatments was determined by resolution of induration and the patient's preparation for further treatment. The volume of ATX-101 injected at each treatment and the interval between treatments were recorded for each patient.

Assessments

Patients provided a medical history and underwent physical/local examination (assessment for edema, numbness, tenderness, bruising, alopecia, and marginal mandibular nerve paresis) at follow-up visits and subsequent treatments. Final follow-up assessments were conducted at least 4 months after the final treatment. Improvement was defined as decreased palpable and/or visible submental fullness because of reduced overall adipose deposits and was based on agreement between evaluations by the patient and the clinician. Injection-site and other adverse events were recorded at each follow-up visit and reported by patients by means of telephone.

Statistical Analyses

A cross-sectional evaluation of data was performed. Categorical variables were summarized as numbers and percentages. Incidence was calculated as the ratio of event count divided by total count.

RESULTS

Data from 167 patients were included in this analysis. Mean patient age was 41.1 years, and 59.9 percent of patients were female (Table 2). Median body mass index was 25.8 kg/m^2 (range, 17.3 to 46.0 kg/m^2).

Because of expansion of the treatment area beyond that defined in the package insert, six patients included in this analysis required an increased number of ATX-101 treatments or volume per session to fully resolve their submental fat. The total number of ATX-101 treatments received by each patient ranged from 1 to 8, with a mean of 2.1 ± 1.1 treatments (Table 3). The volume of ATX-101 injected at each session ranged from 1.2 to 15.0 ml. The total volume of ATX-101 administered to each patient ranged from 4.0 to 58.0 ml. Additional treatment parameters are shown in Table 3.

Improvement in submental fullness was achieved in 160 of 167 patients (95.8 percent). Of the seven patients who did not achieve an improvement, five underwent one ATX-101 treatment and two underwent two treatments. The lack of response in these patients is attributed to an insufficient number of treatments. For patients who received one ATX-101 treatment, the reason for ending treatment was financial (n = 3), concerns with social downtime and deciding to focus on other procedures (n = 1), or not satisfied with results (n = 1). For patients who underwent two treatments (n = 2), neither were satisfied with results; however, one patient went on to receive a third treatment (after the study period), which resulted in an improvement in submental fullness. Representative photographs of expanded safe zone–treated patients are shown in Figure 3.

The majority of patients experienced injection-site edema (lasting from 1 to 40 days), numbness (1 to 71 days), and tenderness (1 to 33 days) (Table 4). Only 28 of 167 patients (16.8 percent) had bruising. Alopecia was experienced by seven of 167 patients (4.2 percent) and resolved with a median duration of 143 days (range, 55 to 204 days). Marginal mandibular nerve paresis was experienced by eight of 167 patients (4.8 percent) and resolved with a median duration of 27 days (range, 14 to 40 days). All events of marginal mandibular nerve paresis occurred during the first session. For patients experiencing marginal mandibular nerve paresis, five of eight (62.5 percent) were treated in zones S1 and S2, whereas three of eight (37.5 percent) were treated in zones S1, S2, and S3.

Table 2. Demographic and Baseline Characteristics

Characteristic	Value (%)
No. of patients	167
Age, yr	
Mean ± SD	41.1 ± 11.5
Range	21–76
No. of women	100 (59.9)
Mean BMI ± SD, kg/m^2	26.0 ± 4.3

BMI, body mass index.

Table 3. ATX-101 Treatment Parameters

Characteristic	Value
No. of patients	167
Mean no. of ATX-101 treatments ± SD	2.1 ± 1.1
Mean interval between ATX-101 treatments ± SD, wk	14.7 ± 17.4
Mean total volume of ATX-101 injected per treatment ± SD, ml	6.9 ± 2.1
Mean total volume of ATX-101 injected per patient ± SD, ml	14.7 ± 8.8

ATX-101, deoxycholic acid injection.

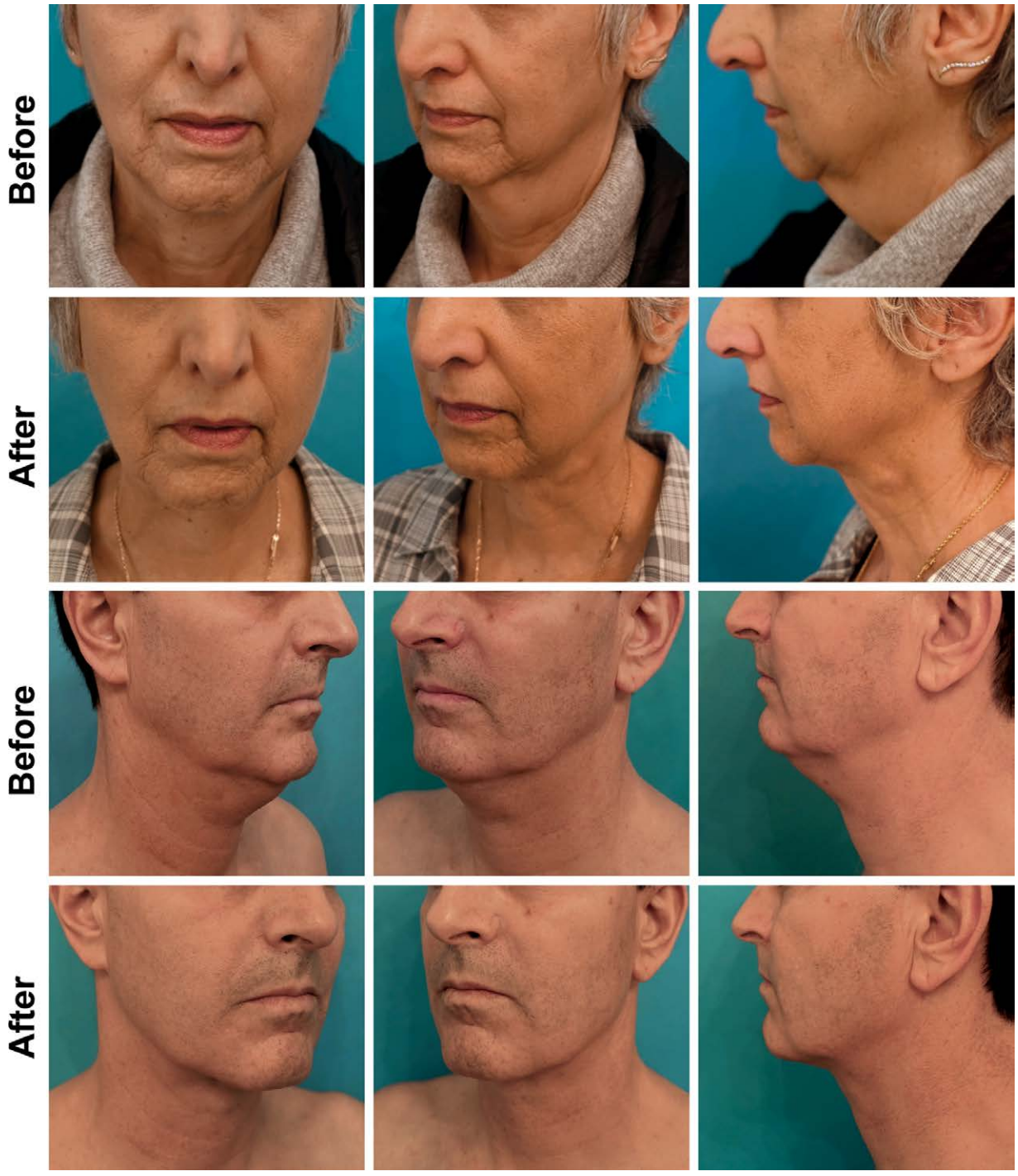

Fig. 3. Representative before-and-after photographs of ATX-101–treated patients. (*Above*) A 62-year-old female patient who received two ATX-101 treatments. ATX-101 was injected in zones S1, S2, and S4 at each treatment (6 ml/treatment; total volume, 12 ml). (*Second row*) Photographs were taken 65 days after the last treatment. (*Third row*) A 55-year-old male patient who received two ATX-101 treatments. ATX-101 was injected in zones S1, S2, and S3 at each treatment (10 ml/treatment; total volume, 20 ml). (*Below*) Photographs were taken 6 months after the last treatment.

DISCUSSION

This analysis is the first to describe a novel expansion of the approved ATX-101 central submental treatment area based on our understanding of submental fat compartments. This technique facilitates patient-centric treatment that

Table 4. Incidence and Duration of Injection-Site Adverse Events*

Adverse Event	Incidence (%)	Mean Duration ± SD, days
Edema	166 (99.4)	6.9 ± 4.4
Numbness	163 (97.6)	29.2 ± 11.5
Tenderness	160 (95.8)	4.9 ± 4.0
Bruising	28 (16.8)	NA
Paresis	8 (4.8)	27.0 ± 9.7
Alopecia	7 (4.2)	126.7 ± 57.3

NA, not available.
*n = 167.

fits individual anatomy, thereby providing more comprehensive therapy for patients who have previously been undertreated. The results presented here demonstrate improvement in submental fullness in the majority of patients with use of the expanded safe zone. In some patients where submental fat is contiguous with jowling from fat flow across the mandible, improvement may be seen because of the contracture that occurs with ATX-101 treatment.

Expanding the submental treatment zone has the potential to increase adverse events, especially marginal mandibular nerve paresis. Compared with the phase 3 randomized controlled trial data for central submental fat treatment, expanded safe zone treatment produced a similar adverse event profile with regard to marginal mandibular nerve paresis (4.3 percent[5–7] versus 4.8 percent), which resolved in a similar period (range, 7 to 60 days[5] versus 14 to 40 days) without sequelae. Expanding the treatment area without increasing the incidence of marginal mandibular nerve paresis was achieved by remaining greater than 2.0 cm below the mandible at injection sites lateral to the central submental fat. The cervical branch of the facial nerve is inferior to the marginal mandibular nerve and innervates the platysma.[12] Injury to the cervical branch can impair the ability of the platysma to add its depressing force to the corners of the mouth, thus producing a similar paresis as that observed with marginal mandibular nerve paresis (termed pseudoparalysis of the marginal branch).[12] Injury to the cervical branch after ATX-101 injection of the on-label submental area has been reported.[13] Thus, we cannot exclude the possibility that some of the observed paresis events in our study were caused by injury to the cervical branch of the facial nerve as opposed to the marginal mandibular nerve.

Bruising was reported in fewer patients in the current analysis (16.8 percent) compared with the randomized controlled trials (71.7 percent).[1] This may be attributable to the postinjection use of ice in all of our patients. Rates of edema and numbness were higher in this analysis than in the randomized controlled trials (99.4 percent versus 87.3 percent and 97.6 percent versus 66.5 percent, respectively), likely because of the increased surface area treated and increased total volume of ATX-101 administered. All adverse events were transient, with most resolving within 1 month, similar to the randomized controlled trials.

Limitations of the current analysis include a restricted patient population (single private practice), lack of a control group, and lack of data related to treatment surface area, which directly correlates with the amount of ATX-101 injected into the anatomical zones. In addition, treatment plans were likely influenced by variable patient satisfaction or limited by cost, thereby precluding direct correlation of treatment plan with patient anatomy. Future studies could correlate surface area treated with objective outcomes and adverse events in a prospective manner to better assess the safety and efficacy of treating patients with ATX-101 using the expanded safe zone, potentially compared with traditional central submental fat treatment.

CONCLUSIONS

The results of this analysis show the feasibility and initial safety and efficacy of expanding the treatment area when using ATX-101 for submental contouring. This individualized plan may result in better outcomes and no increased incidence of adverse events compared with the current one-size-fits-all approach for ATX-101 treatment.

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PATIENT CONSENT

Patients provided written consent for the use of their images.

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