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Current Trends in Management of Submental Liposis
A Pooled Analysis and Survey

Sagar Patel, MD; Russell Kridel, MD

IMPORTANCE Since its approval by the US Food and Drug Administration for treatment of moderate to severe submental liposis in April 2015, deoxycholic acid (Kybella) has received significant media attention as a novel aesthetic treatment. Four phase 3 clinical trials have published data demonstrating the safety and efficacy of the drug compared with placebo; however, no study has juxtaposed the product with submental liposuction.

OBJECTIVE To evaluate the efficacy of injectable deoxycholic acid in the treatment of isolated submental liposis.

EVIDENCE REVIEW A pooled analysis of the data from the 2 European and 2 North American phase 3 clinical trials was performed by grouping the study participants by treatment arm to analyze efficacy, adverse effects, and treatment variables. Members of the American Academy of Facial Plastic and Reconstructive Surgery (AAFPRS) were also surveyed regarding their clinical use of deoxycholic acid, fees, and adverse events.

FINDINGS The pooled analysis included 1738 unique patients (348 men [20.0%] and 1390 women [80.0%]; mean [SD] age, 47.7 [1.6] years) and revealed that all studies demonstrated efficacy compared with placebo. However, a significant number of patients experienced pain, edema, and numbness after injection. The clinical trial population was injected with a mean (SD) of 186.0 (106.6) mg of drug per patient during the course of treatment. A total of 102 members responded to the survey, representing 4% of AAFPRS membership. Based on the results of the survey, clinicians reported charging a mean (SD) of $691.04 ($168.68) per 20-mg vial of deoxycholic acid, resulting in a cost of $6426.35 per study participant. The survey revealed a mean (SD) total cost to the patient for submental liposuction to be $2976.56 ($1041.62).

CONCLUSIONS AND RELEVANCE Although the clinical trials demonstrated functional drug efficacy, the large volume of drug used precluded cost-effectiveness. The survey found clinical practice to differ from the protocols used in the trials. Deoxycholic acid may be only fiscally efficacious for patients with mild to moderate submental liposis who require only 20 to 30 mg of drug per treatment for 3 treatment sessions.

LEVEL OF EVIDENCE 1.

Author Affiliations: Facial Plastic Surgery Associates, Houston, Texas (Patel, Kridel); Department of Otolaryngology–Head and Neck Surgery, University of Texas Health Sciences Center, Houston (Kridel).

Corresponding Author: Russell Kridel, MD, Facial Plastic Surgery Associates, 6655 Travis St, Ste 900, Houston, TX 77030 (rkridel@todaysface.com).

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Isolated submental liposis presents an enticing opportunity in facial and plastic surgery because a reduction can alter facial contours and provide a significant improvement to the frontal and profile views. An aesthetically pleasing jawline often relies on reduction of submental fat. Historically, the problem has been addressed with liposuction in a variety of forms. Ilouz[1] first described the use of a 5-mm cannula and a lateral approach to fat elimination of the body in 1979. Hetter[2] later described the use of a smaller cannula through the submental approach and the addition of infralobular incisions, which improved the contours of the postoperative result.[3] As the procedure has evolved, an emphasis on improving safety and using adjunctive treatments to provide skin tightening have augmented the results of well-performed submental liposuction. Although the procedure is often performed in conjunction with a face-lift to address the aging face, it is also performed alone to improve hereditary isolated submental fat deposition that can create the impression of an overweight face. As evident in other aesthetic procedures, treatment of submental liposis has evolved from the operating room toward a less invasive approach.

In April 2015, the US Food and Drug Administration approved the use of a formulation of synthetic (nonanimal and nonhuman) deoxycholic acid (Kybella; Allergan Plc) for the treatment of moderate to severe submental fat.[4] To date, multiple North American and European phase 3, double-blinded clinical trials have been performed.[5-9] These trials have manifested an excellent safety profile and significant clinical efficacy of sodium deoxycholate acid injection, known as ATX-101 in the clinical studies. The following review provides a pooled analysis of the results of these trials, specifically describing the efficacy of the phase 3 clinical trial data compared with submental liposuction and an analysis of current use of the product among facial plastic surgeons.

Key Points

Question Is the treatment of submental liposis with deoxycholic acid superior to submental liposuction?

Findings Among 1738 unique patients in this pooled analysis of 4 phase 3 clinical trials of deoxycholic acid, a cost analysis demonstrated that each patient in the deoxycholic acid group received a mean of 186 mg of the drug, which equates to a mean cost of $34.55/mg or a mean fee of $6426.35 per patient. Deoxycholic acid is fiscally efficacious for patients with mild to moderate submental liposis who will require 20 to 30 mg of drug per treatment for 3 treatment sessions for a total of 60 to 90 mg.

Meaning For patients requiring large amounts of deoxycholic acid, surgical liposuctions might be a more economical treatment modality.

Methods

We began by performing an analysis of the 2 European and 2 North American phase 3 trials.[5-9] Available data from the studies were pooled and analyzed. In addition, Allergan Plc provided unpublished data from each of the cohorts.

We used 2-sample paired *t* tests to determine whether a statistical difference existed in the percentage of patients who experienced pain, numbness, bruising, and edema between the placebo and pooled ATX-101 treatment groups. An online survey was emailed to all 2700 members of the American Academy of Facial Plastic and Reconstructive Surgery (AAFPRS). Respondents were asked about their current management of submental liposis, including techniques and costs, and queried regarding their experience with deoxycholic acid. Demographic data were also collected. Results were organized in Google Forms and analyzed in Excel software (version 2010; Microsoft Corp). $P < .05$ indicated significance.

Results

A pooled analysis of 4 unique phase 3 trials of ATX-101 including 1738 unique patients (348 men [20.0%] and 1390 women [80.0%]; mean [SD] age, 47.7 [1.6] years) demonstrated 2 distinct, randomized clinical study designs. In the European studies,[5,8] participants were randomized to receive the study treatment in doses of 1 or 2 mg/cm^2 for a maximum of 4 treatment sessions. In the North American studies,[6,7] all participants received the study treatment at a dose of 2 mg/cm^2 for a maximum of 6 treatment sessions. The treatment arm included 997 patients, whereas the control group had 745 who received placebo injections. The pooled study population had a weighted mean (SD) body mass index (calculated as weight in kilograms divided by height in meters squared) of 27.9 (1.9) (**Table 1**). All the studies individually reported an unbiased randomization of populations.

The primary efficacy end points of the studies were addressed using a Submental Fat Rating Scale (range, 0-4, with

Table 1. Demographic Summary of Pooled Phase III Trial Analysis

Source	No. of Patients			Mean (SD) BMI	Female, %	Mean (SD) Age, y
	Total	Placebo Group	ATX-101 Group			
Jones et al,[7] 2016	506	250	256	29.3 (4.4)	421 (83.2)	49.5 (9.3)
Humphrey et al,[6] 2016	516	258	258	29.3 (4.6)	445 (86.2)	47.9 (9.2)
Ascher et al,[5] 2014	360	117	243	26.3 (2.7)	259 (71.9)	46.0 (9.9)
Rzany et al,[8] 2014	362	122	240	25.7 (2.9)	277 (76.5)	46.4 (10.3)
Pooled data	1738	745	997	27.9 (1.9)	1390 (80.0)	47.7 (1.6)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

Table 2. Results of Pooled Analysis of Phase 3 Clinical Trials[a]

Outcome	No. (%) of Patients		*P* Value[c]
	Placebo Arm	ATX-101 Arm[b]	
All patients	745 (100)	997 (100)	.16
Completion of treatment	620 (83.2)	703 (70.5)	.15
Improvement in SFRS score >1 point	248 (33.3)	700 (70.2)	.003
Pain	224 (30.1)	763 (76.5)	.004
Bruising	468 (62.8)	636 (63.8)	.20
Numbness	34 (4.6)	575 (57.7)	.001
Edema	210 (28.2)	601 (60.3)	<.001

Abbreviation: SFRS, Submental Fat Rating Scale.

[a] Data provided by Allergan Plc outside the published phase 3 data.

[b] Indicates deoxycholic acid.

[c] Calculated using paired *t* test evaluating whether a statistical difference existed between the percentages of patients in each arm.

Table 3. Breakdown of Treatment Sessions and Mean Dosage of Drug[a]

Variable	Treatment Arm[b]	
	Placebo	ATX-101[c]
No. of treatment sessions		
1	28	120
2	29	50
3	25	65
4	229	416
5	20	40
6	411	304
Total No. of treatments, mean (SD)	4.9 (0.4)	4.1 (0.5)
Total drug received, mean (SD), mg	0	186.0 (106.6)

[a] Data provided by Allergan Plc outside the published phase 3 data.

[b] Unless otherwise indicated, data are expressed as number of patients.

[c] Indicates deoxycholic acid.

higher scores indicating a visually assessed very large amount of chin fat) performed by the patient and a blinded physician.[5-9] At 12 weeks after the final treatment, the proportion of treatment responders (>1-point improvement in the 5-point clinician-reported Submental Fat Rating Scale) was found to be significantly greater for the ATX-101 groups (700 patients [70.2%]) than the placebo groups (248 patients [33.3%]; $P = .003$) in all studies (**Table 2**). The mean (SD) number of treatment sessions that each participant underwent was 4.1 (0.5). In the total treatment arm, each patient received a mean (SD) dose of 186.0 (106.6) mg of ATX-101 (**Table 3**).

For the survey of the members of the AAFPRS, 102 responses were recorded, representing 4% of the AAFPRS membership. The cohort was balanced in regard to practice location, academic vs private practice, and years in practice (**Figure 1**). Overall, 65 AAFPRS respondents (63.7%) offered deoxycholic acid in their practice at the time of the survey. Three respondents previously offered it but then stopped using it secondary to cost and effectiveness. Of the 102 respondents, 88 (86.3%) stated that they performed the injections.

In regard to treatment protocol, 96 physicians who responded (94.1%) used a mean of 2 to 3 treatments, yielding a weighted mean (SD) number of 2.6 (0.6) injection sessions per patient. Average treatment sessions were scheduled from 3 to more than 6 weeks apart, with the largest number of respondents (49 [48.0%]) scheduling sessions 6 weeks apart. In regard to cost, a weighted mean (SD) cost to the patient was $691.04 ($168.68) per vial (20 mg/2 mL) of deoxycholic acid (**Figure 2**A). Fifty-eight physicians (56.9%) stated that treatment cessation occurred at positive end points, including the patient being satisfied with treatment results or an absence of residual fat available for further treatment. Of interest, 28 respondents (27.4%) stated that the most common reason for treatment cessation was secondary to cost to the patient. The weighted mean (SD) total cost reported by surgeons to perform submental liposuction (including surgeon's fees, anesthesia, and facility fees) was $2976.56 ($1041.62) (Figure 2B).

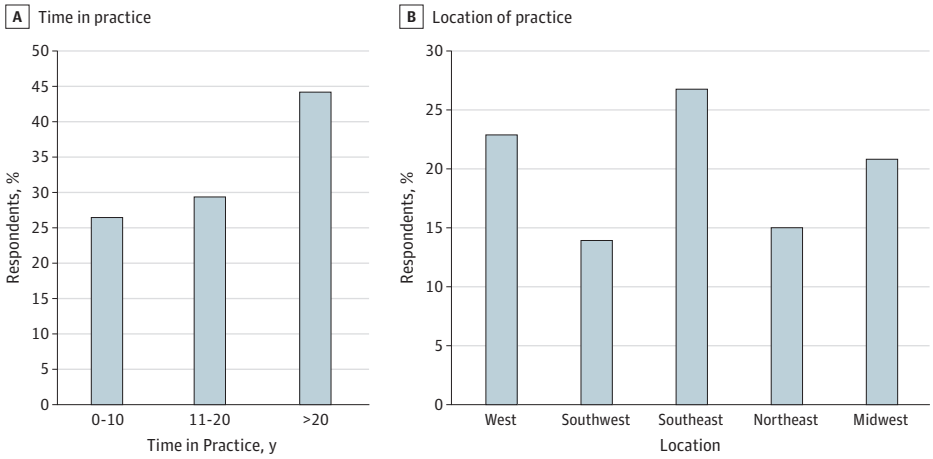
Discussion

Although submental liposuction has long been the standard of care for addressing submental liposis, the advent of deoxycholic acid presents an intriguing option to patients. The current phase 3 studies mention submental liposuction as an alternative treatment; however, despite commenting on the efficacy of deoxycholic acid, none directly compares the 2 treatment modalities. With national television spotlights and extensive coverage from print media,[10-13] deoxycholic acid has been portrayed as a novel wonder drug. Inherent in its quality as an injectable, deoxycholic acid portrays a shorter and easier recovery and less risk than surgical intervention to the average consumer. A similar perception is also that deoxycholic acid would cost less than a surgical procedure, such as submental liposuction.

A detailed review comparing the recovery time and adverse effects of deoxycholic acid and submental liposuction requires a subjective approach. Although the ATX-101 clinical trials demonstrate an overall excellent safety profile, the common adverse effects of treatment are quantified but not qualified by severity. The data demonstrate that a significant number of patients experience pain, transient bruising, edema, and numbness. Given the subjective and variable nature of this experience and that of postliposuction recovery, the 2 are difficult to compare statistically. A literature review also identified minimal studies[14] outlining specific adverse events and complication rates of isolated submental liposuction. Further research, even retrospective reviews, are needed to help define complication rates and recovery from submental liposuction.

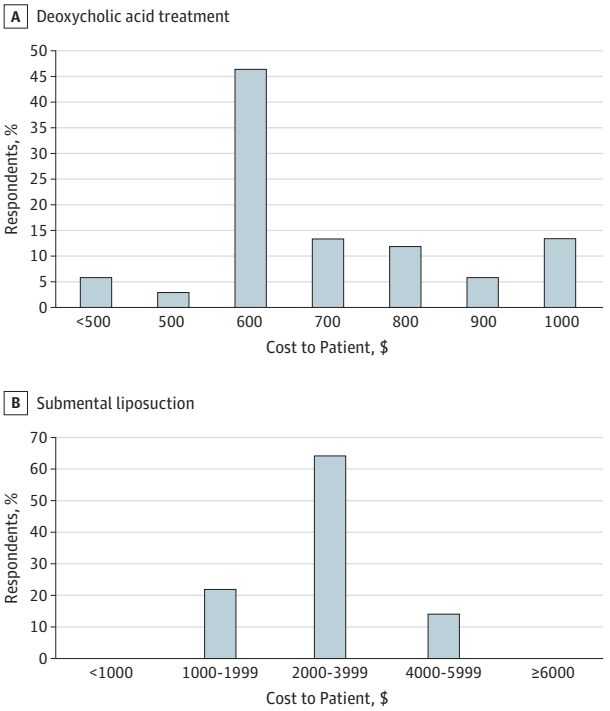
Although each patient experiences a variable recovery process, in our practice, we have witnessed nonquantifiable, comparable postprocedure outcomes in regard to swelling, bruising, and pain for both treatment modalities. This variability

Figure 1. Characteristics of Respondents to Survey of the American Academy of Plastic and Reconstructive Surgery



A total of 102 responses were included in the analysis.

Figure 2. Costs of Treatment of Submental Liposis to Patients



A total of 67 responses to the following questions were included in the analysis: "How much do you charge for a vial of Kybella (20 mg/2 mL)?" (A) and "What is the average cost of submental liposuction (including surgeon's fees, facility fees, and anesthesia, if used)?" (B).

makes it difficult to compare them; however, several advantages of each modality are evident. Although deoxycholic acid almost always necessitates multiple treatments with a considerable duration between sessions, liposuction is almost always a single-modality treatment with an earlier final result. Other advantages of liposuction include the ability to perform a more lateral removal of fat because deoxycholic acid is only injected centrally to avoid injury to the marginal mandibular nerve, which was reported to be transient but as high as 4% in the phase 3 trials.[5-8] Although liposuction can be performed with local infiltrative anesthesia, it often requires mild to moderate sedation for the wary patient. In addition, surgical incisions are required for liposuction, although we have found the incisions are well tolerated and have not required revision, even when visible, because incisions are limited to less than 1 cm and well hidden in the submental crease and earlobes.[15]

Our study also identified several cost considerations that must be addressed when presenting patients with the options of deoxycholic acid injection vs submental liposuction. This issue was of particular importance to patients, as evident in Google Trends data,[16] in which the top related search term associated with deoxycholic acid was *cost*.

An analysis of the estimated cost to treat the patients in the ATX-101 clinical trials[7] can be performed. The clinical trial population was injected with a mean of 186.0 mg of drug per patient. Based on the results of our survey, the average clinician charges $691.04 per 20-mg vial of deoxycholic acid, which would result in an average cost of $6426.35. In a comparative cost analysis, a weighted mean of the survey responses revealed an average total cost of liposuction of $2976.56.

Our survey also found that common practice is different than the protocols established in the phase 3 trials. The weighted mean number of injections administered as reported in our survey was 2.6 treatment sessions compared with the 4.1 injections administered in the trials. Our survey did not address how many vials per treatment session were used for an average patient in clinical practice. This determination was based on the surface area of the safe injection zone bound by the anterior digastric muscles and the region above the hyoid bone. Although this area is variable in each patient, it is closely correlated with sex and body mass index. We believe that this area is the keystone variable in preoperative analysis that helps a clinician determine whether deoxycholic acid would be a cost-effective treatment modality. Our data show that patients who only

require 1.0 to 1.5 vials of deoxycholic acid (20-30 mg) per session can obtain cost efficacy. The mean cost of treatment, assuming 1 vial per session and 2.6 sessions, would be $1796.72.

Limitations

Our analysis is limited primarily by the lack of previous statistical studies on submental liposuction and the difficulty of standardizing a typical postoperative course to allow for head-to-head comparison. Statistically, our survey did not provide us with a benchmark of accuracy equal to the data presented in the phase 3 trials. Ideally, a prospective study would incorporate the mean milligrams of drug injected per patient by each survey respondent. Previous literature on submental liposuction discussed the array of complications but did not quantify the resulting recovery period.[14,15] In addition, our survey did not encompass the diverse specialty of clinicians who use the product. In a recent publication, Cohen and colleagues[17] identified that deoxycholic acid injection is not without recovery time or potential adverse effects and is not a 1-time treatment. They also recognized that undertreatment as a cost-saving practice can be a potential area of concern for the future of the product.[17] To maximize patient satisfaction and reduce the number of patients in whom treatment cessation is based on cost limitation, our study helps guide clinicians in performing a cost-efficacy analysis for each potential patient.

Conclusions

Although patients are often averse to surgery, the clinicians are responsible (whether they provide both services) for discussing the risks and benefits of and alternatives to any proposed treatment. Although the US Food and Drug Administration indication for deoxycholic acid is moderate to severe submental fat reduction, we propose that deoxycholic acid is better suited for patients with mild to moderate submental liposis, and cost efficacy should be discussed after an estimation of how many vials will be needed in each session to be performed. If the cost of the drug to the patient decreases and the safety profile is further manifest, deoxycholic acid may become more popular. This study suggests that clinicians consider submental liposuction as a superior alternative in regard to cost and recovery for patients who will require more than 2 vials per treatment and more than 3 treatment sessions.

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Author Contributions: Dr Patel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Both authors.
Acquisition, analysis, or interpretation of data: Patel.
Drafting of the manuscript: Both authors.
Critical revision of the manuscript for important intellectual content: Both authors.
Statistical analysis: Patel.
Obtained funding: Patel.
Administrative, technical, or material support: Both authors.
Study supervision: Both authors.

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Additional Contributions: Allergan provided some unpublished data and associated statistical analysis from each of the phase 3 studies at our request. The specific data provided that were not included in the phase 3 trials consisted of a table depicting the mean amount of drug (in milligrams and milliliters) received per patient in each of the trials. Allergan Plc was given the opportunity to review the manuscript for medical accuracy before submission because the clinical trial data were theirs; however, we maintained complete control of the content. No funds or fees were paid by Allergan for this study. We thank the American Academy of Facial Plastic Surgery and its members who participated in the survey. Hayden Sakow, BA, Ruby Angiolillo Designs, provided his editorial assistance, for which he was not compensated.

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