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REVIEW ARTICLE

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The development, evidence, and current use of ATX-101 for the treatment of submental fat

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Summary

ATX-101 (deoxycholic acid) is the first pharmaceutical therapy approved by the FDA for the reduction in submental fat. Deoxycholic acid is an endogenous secondary bile acid that normally solubilizes dietary fat, contributing to its breakdown and absorption within the gut. This article reviews the identification of deoxycholic acid as a lipolytic agent, and the mechanism of action, pharmacokinetics, and pharmacodynamics of ATX-101. In addition to phase I/II trials, four Phase III clinical trials have evaluated safety and efficacy of ATX-101. These studies helped establish the appropriate dosage, administration techniques, warnings, and side effects of ATX-101. ATX-101 is effective in treating submental fat. Adverse events, although common, are mild and transient.

KEYWORDS

ATX-101, deoxycholate, deoxycholic acid, Kybella, submental fat

1 | INTRODUCTION

The presence of submental fat may be due to a combination of aging, lifestyle, and diet; however, genetic predisposition also appears to play a large role. For these patients, the submental fat or "double chin" may have negative impact in the workplace or social endeavors. The loss of chin profile with unwanted submental fat (both superficially and deep to the platysma muscle) may be of particular concern to some patients. Until recently, liposuction and cosmetic surgery were considered the mainstay for elimination of unwanted submental fat. However, due to prolonged recovery times, and risk of contour irregularities, excess skin, and infections, other noninvasive options are desirable. Despite numerous advances in noninvasive cosmetics, there are few options with a relative paucity of evidence to re-contour submental fat nonsurgically.[1-6]

Deoxycholic acid is an endogenous secondary bile acid that normally solubilizes dietary fat, contributing to its breakdown and absorption within the gut. It was originally observed to treat the accumulation of localized fat through adipocytolysis in cell culture. Moreover, deoxycholic acid was noted to target fat cells specifically without injury to skin or muscle. Following these observations, Kythera Biopharmaceuticals, Inc. (Westlake Village, CA, USA), developed a synthetic form of deoxycholic acid, ATX-101 (Kybella).[7]

The clinical development program for ATX-101 included 18 phase I to III treatment studies, which investigated the indication for submental fat.[8] The evaluation of deoxycholic acid to treat submental fat began in 2007 by assessing side effect profiles. Safety data from these studies showed that injections of deoxycholic acid did not drastically or dangerously alter plasma concentrations of endogenous compounds. Furthermore, deoxycholic acid is excreted rapidly from the body. Phase I and Phase II trials established the optimal ATX-101 dose strength and treatment protocol for reducing submental fat. Finally, four Phase III clinical trials were conducted and are detailed in this review. Data from these trials led to Food and Drug Administration approval of ATX-101 in April 2015. This is the first pharmaceutical intervention approved by the FDA for the reduction in submental fat.

2 | METHODS

A review of the literature was performed through PubMed. Keywords utilized included deoxycholic acid, ATX-101, and submental fat. Overall, 20 sources were originally selected for review, and additional sources from the original source bibliographies were used to further supplement this review.

2.1 | Preclinical data

Rotunda et al., having noted that phosphatidylcholine injections were being used increasingly off-label for localized deposits of fat, sought

to characterize the mechanism of action. The authors performed cell membrane lysis assays on porcine cell cultures treated with phosphatidylcholine, isolated sodium deoxycholate, or common laboratory detergents. Phosphatidylcholine, more specifically through its constituent sodium deoxycholate activity, worked primarily as a detergent causing nonspecific lysis of cell membranes.[9] Gupta et al.[10] confirmed these findings using rabbit dorsal fat pad tissue. Sodium deoxycholate was found to be almost as effective as phosphatidylcholine in reducing the viability of mature adipocytes over time.

Thuangtong et al. then sought to characterize why sodium deoxycholate might preferentially target fat cells. In vitro models showed that sodium deoxycholate injected into fat tissue caused adipocyte death; however, other cell types were less affected. The authors reported that physiologic concentrations of albumin or other protein rich tissue decreased overall activity of sodium deoxycholate. Therefore, it was postulated that adipocytes may be preferentially targeted in vivo due to paucity of protein binding and inactivation.[11]

2.2 | Phase I

Walker et al. investigated the safety and pharmacokinetics of the maximal therapeutic dose of ATX-101 (100 mg). In this study, 24 patients with prior measurements of endogenous deoxycholic acid plasma levels received subcutaneous injections of ATX-101 (2 mg/cm^2) into submental fat. Pharmacokinetic evaluation was then repeated periodically over 24 hours. In these patients, deoxycholic acid plasma concentrations peaked rapidly and returned to baseline endogenous values within 24 hours. The most common adverse events were injection-site pain, edema, erythema, and hematoma, which were temporally related to the day of dosing and mild to moderate in severity.[12]

Subsequently, Walker and Lee sought to further characterize the safety, pharmacokinetics, and pharmacodynamics of ATX-101. Following baseline evaluation of endogenous deoxycholic acid, lipids, and adipokines, 10 patients received subcutaneous injections of ATX-101 into abdominal fat. Subsequent plasma studies did not show a statistically significant change in total cholesterol, total triglycerides, free fatty acids, C-reactive protein, or interleukin-6. Adverse events were mild and transient.[13]

Histological data from a multicenter, open-label Phase I study provided support for the postulated mechanism of action of deoxycholic acid. In this study, ATX-101 was injected into subjects' abdominal fat pads at different time points prior to planned abdominoplasty, and tissue biopsies were examined microscopically. It was found that ATX-101 exerts its primary effect, adipocytolysis, as early as day 1. Subsequently neutrophils invade tissue (day 3), followed by macrophages (day 7), followed by fibroblasts (day 28). At day 28, inflammation largely resolves, providing the rationale for the approved 1-month time intervals between each treatment.[7,8]

2.3 | Phase II

Two multicenter, randomized, double-blind, placebo-controlled studies (NCT00618722 and NCT00618618) demonstrated that a 2 mg/cm^2 dose of ATX-101 consistently resulted in greater efficacy relative to a 1-mg/cm^2 dose. Furthermore, these studies showed that a higher 4 mg/cm^2 dosing did not produce greater efficacy and resulted in more frequent and severe and adverse events. In these studies, the dose of 2 mg/cm^2 was achieved via 0.2-mL injections spaced at 1-cm intervals within the submental fat pad. This is now the approved treatment protocol for ATX-101.[8,14]

Phase III clinical trials are based primarily upon the Patient-Reported Submental Fat Rating Scale (PR-SMFRS) (Table 1), the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) (Table 2), and the Patient-Reported Submental Fat Impact Scale (PR-SMFIS) (Table 3). These endpoints were originally validated in a Phase II dose-ranging study by Dover et al. Moreover, these authors established a reproducible MRI protocol for measuring reduction in submental fat after ATX-101 treatment.[15]

2.4 | Phase III

The REFINE-1 trial (NCT01542034) included 506 patients with moderate-to-severe submental fat randomized to ATX-101 or placebo for up to six treatment sessions (Table 4). Subjects were

TABLE 1 Patient-reported submental fat rating scale[15–17]

5-Point scale:
0=No chin fat at all
1=Slight amount of chin fat
2=Moderate amount of chin fat
3=Large amount of chin fat
4=Very large amount of chin fat

TABLE 2 Clinician-reported submental fat rating scale[15-17,22]

5-Point scale:
0=No submental convexity, no localized fat
1=Mild submental convexity, minimal localized SMF
2=Moderate submental convexity, prominent localized SMF
3=Severe submental convexity, marked localized SMF
4=Extreme submental convexity

SMF, Submental fat.

TABLE 3 Patient-reported submental fat impact scale[16,17]

11-Point scale (lower scores indicate improvement or reduced negative impact):
Psychological impact on self-perception of six emotional and visual characteristics related to submental fat appearance was investigated:
1. How happy are you with the appearance of your own chin fat?
2. How bothered are you by the appearance of your own chin fat?
3. How self-conscious are you about the appearance of your own chin fat?
4. How embarrassed are you about the appearance of your own chin fat?
5. How much older do you look because of your chin fat?
6. How much overweight do you look because of your chin fat?

TABLE 4 Comparison of four Phase III, clinical trials evaluating ATX-101 vs placebo injections[16-19]

Trial	Number of patients	Number of treatment sessions	Duration of study (wk)	Primary endpoint(s) achieving statistical significance	Secondary endpoint(s) achieving statistical significance	Percent of treatment group with adverse events (%)
REFINE-1	506	6	12	CR-SMFRS/PR-SMFRS ≥1-point improvement; CR-SMFRS/PR-SMFRS a ≥2-point improvement	>10% reduction in SMF on MRI[a]; reduction from baseline in the psychological impact of submental fat based on the PR-SMFIS	84.3
REFINE-2	516	6	12	CR-SMFRS/PR-SMFRS ≥1-point improvement; CR-SMFRS/PR-SMFRS a ≥2-point improvement	>10% reduction in SMF on MRI[b]; reduction from baseline in the psychological impact of submental fat based on the PR-SMFIS	85.7
Rzany, et al.	363	4	12	CR-SMFRS ≥1-point improvement; proportion of patients satisfied with their appearance (ie, with a score of ≥4 on the SSRS rating scale)	Caliper measurements of submental fat thickness; reduction from baseline in the PR-SMFRS and PR-SMFIS; and the effect of treatment on skin laxity (Skin Laxity Rating Scale, SLRS)	>90
Ascher, et al.	360	4	12	CR-SMFRS ≥1-point improvement; proportion of patients satisfied with their appearance (ie, with a score of ≥4 on the SSRS rating scale)	Reduction from baseline in the PR-SMFRS and PR-SMFIS; and the effect of treatment on skin laxity (Skin Laxity Rating Scale, SLRS)	99.2

CR-SMFRS, Clinician-reported submental fat rating scale; PR-SMFIS, Patient-reported submental fat impact scale; PR-SMFRS, Patient-reported submental fat rating scale.
[a]Subset of 224 patients.
[b]Subset of 225 patients.

predominantly white, female, around 50 years of age, with an average BMI of ~29 kg/m^2. The authors found that more patients treated with ATX-101 achieved a ≥1-point improvement on the 5-point CR-SMFRS/PR-SMFRS after 12 weeks as compared to those treated with placebo (70% vs 18.6%, P<.001). Similarly, more patients treated with ATX-101 2 mg/cm^2 achieved a ≥2 grade change in the CR-SMFRS/PR-SMFRS scale than those patients treated with placebo (13.4% vs 0%, P<.001). Among the 224 patients monitored via MRI, the proportion of ATX-101-treated patients who achieved 10% reduction was over eight times greater than that of placebo-treated patients (46.3% vs 5.3%; P<.001). Adverse events were primarily local reactions (84.3% ATX-101 group vs 69.0% placebo group), were highest following the first treatment, and diminished with subsequent treatment sessions.[16]

The REFINE-2 trial included 516 patients randomized to ATX-101 2 mg/cm^2 or placebo for up to six treatment sessions. Subjects were predominantly white, female, around 50 years of age, with an average BMI of 29.3 kg/m^2. The authors found that more patients treated with ATX-101 achieved a ≥1-point improvement on the 5-point CR-SMFRS/PR-SMFRS after 12 weeks as compared to those treated with placebo (66.5% vs 22.5%, P<.001). Similarly, more patients treated with ATX-101 2 mg/cm^2 achieved a ≥2 grade change in the CR-SMFRS/PR-SMFRS scale than those patients treated with placebo (18.6% vs 3%, P<.001). Among the 225 patients monitored via MRI, the proportion of ATX-101-treated patients who achieved 10% reduction was greater than that of placebo-treated patients (40.2% vs 5.2%; P<.001). Adverse events were primarily local reactions (85.7% ATX-101 group vs 76.9% placebo group), most resolved within 14 days, and nearly all resolved by end of the study.[17]

In another double-blind Phase III clinical trial, Rzany et al. randomized 363 patients with moderate-to-severe submental fat to receive ATX-101 (1 or 2 mg/cm^2) or placebo injections for up to four treatment sessions. At the 12-week follow-up, by the CR-SMFRS criteria, 59.2% of ATX-101 1 mg/cm^2 treated patients and 65.3% of 2 mg/cm^2 treated patients reached the primary endpoint (compared to 23.0% of placebo). By the Subject Self-Rating Scale (SSRS) criteria used in this study (Table 5), 53.3% of ATX-101 1 mg/cm^2 treated patients and 66.1% of 2 mg/cm^2 treated patients reached the primary endpoint (compared to 28.7% of placebo). Additionally, caliper measurements showed a statistically significant reduction in submental fat. Adverse events were seen in over 90% of ATX-101-treated patients, compared to 50.8% of patients treated with placebo. Injection-site pain was common in both groups. Other adverse events more commonly reported in the ATX-101 group included swelling, numbness, erythema, and bruising.[18]

In another double-blind Phase III clinical trial, Ascher et al. randomized 360 patients with moderate-to-severe submental fat to

TABLE 5 Subject self-rating scale[18,19]

Overall satisfaction with facial appearance evaluated by 7-point scale:
0=Extremely dissatisfied
1=Dissatisfied
2=Slightly dissatisfied
3=Neither satisfied not dissatisfied
4=Slightly satisfied
5=Satisfied
6=Extremely satisfied
Patients with a score of 4 or higher are considered responders.

receive ATX-101 (1 or 2 mg/cm^2) or placebo injections at up to four treatment sessions. Similar to the previous study, at 12 weeks, by the CR-SMFRS criteria, 58.3% of ATX-101 1 mg/cm^2 treated patients and 62.3% of 2 mg/cm^2 treated patients reached the primary endpoint (compared to 34.5% of placebo). By the SSRS criteria, 68.3% of ATX-101 1 mg/cm^2 treated patients and 64.8% of 2 mg/cm^2 treated patients reached the primary endpoint (compared to 29.3% of placebo). Caliper measurements were not included as a secondary endpoint in this study. Adverse events were similar to previous studies and included injection-site pain, swelling, numbness, bruising, and induration. These were more common in the ATX-101 group (99.2%) than the placebo group (78.9%).[19]

2.5 | Administration

Deoxycholic acid (Kybella) is supplied in 10 mg/mL sterile 2 mL vials. It is administered in 0.2 mL aliquots spaced 1 cm apart, for up to a total of 10 mL at a maximum of 50 injection sites (Table 6). Patients may be treated at 1-month intervals repeated up to six times. The physician should outline the treatment area with a 1-cm grid prior to each session. Pretreatment with topical anesthetic or ice packs may decrease unwanted pain with numerous injection sites. Figure 1 shows a patient treated with 2 mL of deoxycholic acid with a reduction in submental fat after one session. Physicians should also be aware of facial anatomy and injection technique to avoid unwanted complications including paresis of the facial nerve, dysphagia, and superficial ulcerations.[20] In the REFINE-2 trial, marginal mandibular nerve paresis did occur in 4.3% of ATX-101 patients (compared to 0.8% of placebo), with median durations lasting from 7 to 61 days. To prevent marginal mandibular nerve injury, authors have recommended avoiding ATX-101 injections above a line drawn 1.0-1.5 cm below the inferior mandibular border. Dysphagia related to volume of injection is another potential complication physicians should be aware of. In the REFINE-2 trial, this occurred in 2.3% of ATX-101 patients (compared to 0.4% of placebo).[17]

3 | CONCLUSION

ATX-101 is a safe and effective lipolytic agent indicated for the treatment of submental fat. Four Phase III trials reviewing ATX-101 have shown significant reduction in submental fat and augmented visual appearance of the submental area. These findings were confirmed by MRI imaging. ATX-101 treatment also had a positive psychological quality benefit in these trials. Future studies will provide additional data including the long-term efficacy, delayed adverse events, use during pregnancy and lactation, and use in pediatric and geriatric patients. Furthermore, future studies are needed to

TABLE 6 Deoxycholic acid (Kybella): key information[20]

Indication	Deoxycholic acid is indicated for the improvement in the appearance of moderate-to-severe convexity or fullness associated with submental fat in adults.
Dosage	- 0.2 mL injections spaced 1-cm apart - up to 50 injections (10 mL) in a single treatment - up to 6 treatments spaced at 1-mo intervals
Administration	Safe administration depends upon the correct number and locations for injections, proper needle placement, and technique. This includes avoidance of the marginal mandibular nerve, avoidance of the platysma, and the use of a 1 cm injection grid to mark the injection sites.
Storage	Store at 20-25°C (68-77°F)
Contraindications	Deoxycholic acid injection is contraindicated in the presence of infection at the injection sites.
Warnings	Marginal mandibular nerve injury, dysphagia, submental hematoma/bruising
Adverse Reactions	The most common adverse reactions include injection-site edema/swelling, hematoma, pain, numbness, erythema and induration.
Pregnancy	In animal reproduction studies, no fetal harm was observed with the subcutaneous administration of deoxycholic acid to rats during organogenesis at doses up to 50 mg/kg. Drug associated risk has not yet been studied in pregnant women.
Lactation	No information is currently available on the presence of deoxycholic acid in human milk, the effects on a breastfeeding infant or the effects on milk production.
Pediatric Use	Safety and efficacy data in patients under 18 y of age has not yet been established.
Geriatric Use	Clinical trials did not include sufficient numbers of patient aged 65 or older to determine whether clinical responses and adverse events differ in this age group.
Carcinogenesis	Long-term animal or human studies have not been performed to evaluate the carcinogenic potential.

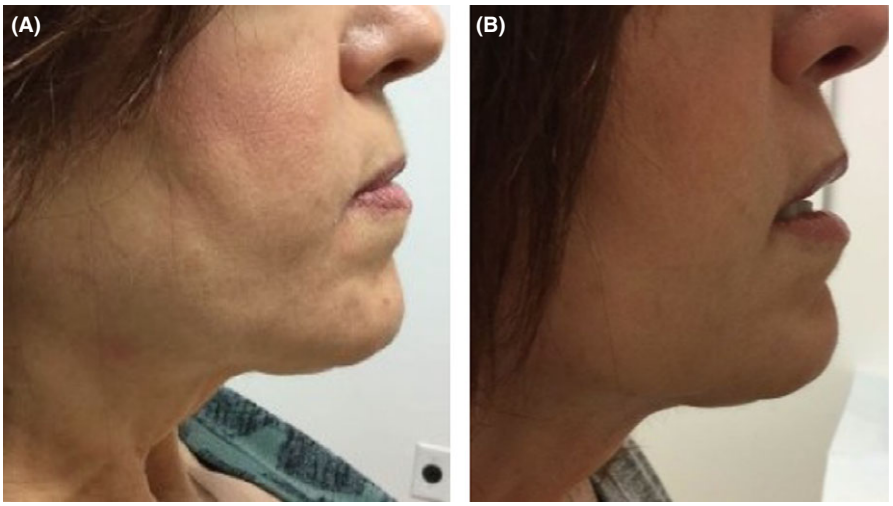

FIGURE 1 Representative patient photographs (A) before (left) and (B) 1 mo after (right) treatment with ATX-101. Total dose 2 mL. Patient expressed satisfaction with results after only one treatment session

investigate additional indications for deoxycholic acid. These may include the improvement of unwanted adipose tissue at other anatomic sites and the nonsurgical treatment of lipomas.

The authors of this review conclude the following:

1. ATX-101 is efficacious in reducing submental fat, confirmed both subjectively via patient and physician grading scales and objectively via MRI and caliper measurements.
2. ATX-101 may require up to six treatments, but the majority of patients experience satisfactory results with four or less treatments.
3. The majority of patients treated with ATX-101 will experience adverse events. Local site injection reactions, specifically injection-site pain, accounts for most of these adverse events, and is often transient and of mild-to-moderate severity. Other adverse events may include bruising, erythema, induration, and numbness. Increased skin laxity has not been observed in Phase III trials[16-19], and this may be due to increased neocollagenesis suggested by tissue fibroblasts observed in Phase I trials.[8]
4. A knowledge of general facial anatomy and injection technique is requisite to avoid more dangerous complications, including marginal mandibular nerve paresis, dysphagia, and superficial ulcerations.
5. In general, ATX-101 at a dose of 2 mg/cm^2 appears to be more efficacious than 1 mg/cm^2 dosing and is equally efficacious to 4 mg/cm^2 dosing with less adverse events.
6. While Phase III study protocols were designed to assess patient response at durations of <1 year, subsequent follow-up of patients from Phase II/III trials has demonstrated maintenance of effect for up to 4 years.[21] Further follow-up is needed to make definitive conclusions on long-term efficacy and delayed adverse events.

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