ORIGINAL ARTICLE

Current status of localized submental fat treatment with sodium deoxicolate (ATX-101)

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ABSTRACT

Aim Facial aesthetics is at present a concept intricately linked to the degree of self-esteem. Unwanted submental fat (SMF) leads to an unattractive submental profile. Sodium deoxicolate (ATX) -101 is the only injectable drug approved to decrease submental fat of moderate to severe intensity.

Methods We carried out a bibliographic review in PubMed using the key words: deoxycholic acid, ATX-101, and submental fat. Only complete articles published between 2009 and 2019, and focused on submental fat were reviewed, excluding those articles relating to that spoke of deoxycholate in the treatment of fat in other locations or in which deoxycholate was associated with other drugs.

Results In several phase III clinical trials, injection of 2 mg/cm2 deoxycholic acid in SMF has reduced moderate-severe fullness compared to the placebo group. These results were maintained in most cases during a long follow-up period. Injections of deoxycholic acid are generally well tolerated, with limited adverse effects in the treatment area, with a mild and complete resolution without sequelae. However, not all patients with SMF are suitable for deoxycholic acid therapy, and therefore a proper selection is very important to achieve the desired aesthetic results.

Conclusion Deoxycholic acid injections are effective and are a generally well-tolerated, minimally invasive option for the treatment of moderate to severe intensity SMF in selected adults.

Key words: adipocitolysis, double chin, lipolysis

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INTRODUCTION

In aesthetic medicine, many treatments are available as a result of the high demand of the population related to dissatisfaction with their body image. Likewise, there are numerous investigations with the objective to maintain standards of facial symmetry and ideal body contours, such as the introduction of new materials and techniques, especially those aimed to eliminate localized fat (1).

Specifically, at facial level, the ideal youthful face shape has been described as an inverted triangle, being wide at the top and progressively narrower from the middle of the face to the chin. The shape and contour of the chin and neck play an important role in facial aesthetics and the accumulation of fat in these areas can make an individual appear to be overweight and look older, causing low self-esteem (1). For this reason, regardless of age, an excess of localized fat in the submental area can represent an aesthetic problem in women and men (2,3) since it can occur as a consequence of aging, genetic predisposition or be related to poor healthy lifestyles, which, in addition, generally do not tend to improve with weight reduction (1,2).

Sodium deoxycholate (ATX) -101was approved in 2015 by Health Canada and the US Food and Drug Administration as an injectable drug for cosmetic purposes in the reduction of submental fat. The development of ATX-101 as a pharmacological treatment for fat reduction was based on the findings of Rotunda et al. (4). From their study, deoxycholic acid (DC) was identified as the most active component responsible for the reduction of adipose tissue (5-7), (8,9) and it is used for the reduction of moderate or severe submental fat in adults.

Deoxycholic acid is a natural constituent of bile salts in humans. Its detergent action derives from its ability to intercalate the hydroxyl residues (-OH) in the hydrophobic zone of the lipid bilayer of the cell´s membrane, causing its disorganization. Specifically, *in vitro* observations showed that its administration on adipose tissue cells caused an alteration of the phospholipid bilayer in the cell membrane and led to the lysis of adipocytes [10].

The administration of the DC solution must be carried out in the submental area, ensuring that there is a sufficient amount of accumulated fat between the dermis and the platysma muscle (preplatysmal fat, more superficial). It needs to be 1 cm of separation between each injection site (up to a maximum of 50 per session). This can be done up to a maximum of 6 sessions, with a minimum separation of at least 4 weeks. Injections should always be made at least 1 cm below the lower border of the mandible (from the angle of the mandible to the chin) and in specifically marked areas where submental fat accumulates (11). Histological studies of tissues treated with DC show that adipocyte lysis occurs on day 1; on day 3 there is evidence of acute local neutrophilic inflammation and macrophage infiltration occurs on day 7. Local inflammation resolves on day 28. All of these data show that DC produces adipocyte lysis, causing a histological phenomenon known as fat necrosis, with massive release of triglycerides into the interstitium that consequently unleashes an inflammatory response with infiltration of macrophages. It has been shown that DC does not cause the destruction of other cells other than adipocytes (2,5).

Another cause of concern related to its use is any possible inflammatory response and damage cause to other vital tissues, such as muscles or nerves. In clinical trials, the inflammatory response after DC infiltration (swelling, erythema, and bruising) has been shown to lead to repeated inflammation and thus potentially fibrosis (2). That is why it is recommended that ATX-101 should be administered within 28-day intervals to allow the resolution of the induced inflammation.

Generally, the adverse effects observed in clinical trials were mostly minor, of small intensity and duration, and resolved without sequelae (2). To minimize adverse effects, it is very important to use a strict ATX-101 injection protocol.

In order to examine the current status of ATX-101 in the treatment of localized adiposities in the submental area, this paper will address, through a bibliographic review, the satisfaction and clinical efficacy of treatments with ATX-101, as well as its safety and possible adverse effects.

It is convenient to clarify some scales that will be mentioned in the results and that served as variables in different studies of the European Union. These scales are: the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) (Figure 1) that measures the severity of submental fat and is scored by a physician; the Subject Self Rating Scale (SSRS) (Table 1) or the assessment of patient satisfaction, and the submental fat score reported by the patients with the Patient-Reported Submental

Table 1. Subject Self Rating Scale (SSRS) for the assessment of patient satisfaction*

Score†	Patient satisfaction
0	Extremely dissatisfied
1	Dissatisfied
2	Slightly dissatisfied
3	Neither satisfied not dissatisfied
4	Slightly satisfied
5	Satisfied
6	Extremely satisfied

* Overall satisfaction with facial appearance evaluated by 7-point scale (12); †Patients with a score of 4 or higher are considered responders

Table 2. Submental fat score reported by the patients with the Patient-Reported Submental Fat Rating Scale (PRSMFRS) (13)

Score	Amount of submental fat
0	No chin fat at all
1	A slight amount of chin fat
2	A moderate amount of chin fat
3	A large amount of chin fat
4	A very large amount of chin fat

Fat Rating Scale (PRSMFRS) was also assessed (Table 2) (12,13) to examine the current status of treatment of localized fat at the submental level with sodium deoxycholate (ATX1010) and to know the safety and most frequent adverse events in clinical practice with ATX101.

MATERIAL AND METHODS

A literature review was conducted through PubMed. Key words used included deoxycholic acid, ATX-101, and submental fat. Only complete papers published between 2009 and 2019 and focusing on submental fat were reviewed, excluding those articles relating to deoxycholate in the treatment of fat in other locations or in which deoxycholate was associated with other drugs (such as phosphatidylcholine).

Twenty sources were originally selected for the review, and additional sources from the original bibliographies were used to supplement this review.

RESULTS

Analysing the articles with ATX101, two phase I trials, two phase II trials and four phase III clinical trials were identified that were used for the analysis.

Walker et al. (2015) (14) investigated the safety and pharmacokinetics of the maximum therapeutic dose of ATX-101 (100 mg). In this study, 24 patients, with previous measurements of endogenous DC plasma levels, received subcutaneous injections of ATX-101 (2 mg / cm2) into the submental fat. Throughout 24 hours, the pharmacokinetics were periodically reviewed and it was observed that the maximum plasma concentration of DC rose rapidly, falling back to baseline endogenous values at 24 hours. The most common adverse events were pain, oedema, erythema, and hematoma at the injection site, which appeared on the same day of the injection and were mild.

In another phase I, multicentre study, Humphrey et al. (15) supported this idea regarding the mechanism of action of DC. Before and after the abdominoplasty, the authors treated abdominal fat with ATX-101 and microscopically examined tissue biopsies. The authors found that ATX-101 exerts its primary effect, adipocytolysis, from day 1. Subsequently, neutrophils invade the tissue (day 3), followed by macrophages (day 7) and followed by fibroblasts (day 28). On day 28, the inflammation resolves, which justifies the approved 1-month time interval between each treatment.

Two multicentre, randomized, double-blind, placebo-controlled studies (16,17) demonstrated that a 2 mg/cm^2 dose of ATX-101 had a consistently higher efficacy over a 1 mg/cm^2 dose. Furthermore, these studies showed that a dose greater than 4 mg/cm^2 does not produce greater efficacy and produces more frequent and serious adverse effects. In these studies, the 2 mg/cm^2 dose was delivered by injections into the 0.2 mL submental fat pad, spaced 1 cm apart. Today, this is the approved treatment protocol for ATX-101.

The REFINE-1 study included 506 patients with moderate to severe submental fat, randomized and treated with ATX-101 or placebo, for a minimum of 6 sessions. The subjects were mostly white, female, with ages around 50 years and an average BMI of 29 kg/m2. The authors found that at 12 weeks most patients treated with ATX-101 achieved an improvement of ≥1 point in 5 categories of the CR-SMFRS PR-SMFRS scales (Figure 1, Table 2) compared to those treated with placebo (70%

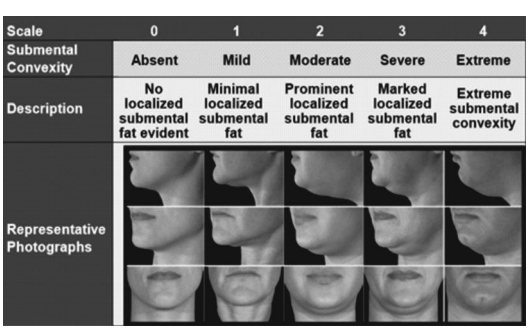

Figure 1. Clinician-Reported Submental Fat Rating Scale (CR-SMFRS) (13) (with the permission of Humphrey S)

vs. 18.6%; p<0.001). Similarly, the majority of patients treated with ATX-101 2 mg/cm^2 achieved an improvement of ≥2 points on the CR-SMFRS/PR-SMFRS scales compared to those treated with placebo (13.4% vs. 0%; p<0.001). Of these, 224 patients were reviewed by magnetic resonance and it was observed that the number of patients treated with ATX-101 who achieved 10% fat reduction was eight times higher than those treated with placebo (46.3% vs. 5.3%; p<0.001). Regarding the adverse effects detected, they were mainly local reactions (84.3% ATX-101 group vs. 69.0% placebo group); more frequent in the first sessions that decreased with subsequent sessions (12).

The REFINE-2 study included 516 randomized patients treated with ATX-101 2 mg/cm^2 or placebo, for a minimum of 6 sessions. Also, in this case, the patients were mostly white, women, around 50 years old and with an average BMI of 29.3 kg/m2. The authors found that a greater number of patients treated with ATX-101 achieved a ≥1-point improvement on the CR-SMFRS/PR-SMFRS scales after 12 weeks, compared to patients treated with placebo (66.5% vs. 22.5%; p<0.001). A total of 225 patients underwent MRI and also in this case, a 10% reduction in fat was observed in most patients treated with ATX-101 compared to placebo (40.2% vs. 5.2%; p<0.001). Adverse events were mainly local reactions (85.7% ATX-101 group vs. 76.9% placebo group); most resolved within 14 days and almost all resolved by the end of the study (13).

Rzany et al. (2014) (18) treated 363 patients with ATX-101 (1 or 2 mg/cm^2) submental fat (moderate to severe grade), compared to placebo injections, for 4 sessions. The primary endpoint was an improvement of ≥ 1 point in the CR-SMFR and ≥4 points in the SSRS (subject self-rating scale) (Table 1). The secondary objective was the reduction of the calibre of the submental fat. After a 12-week follow-up, 59.2% of patients treated with ATX-101 1 mg/cm^2 and 65.3% of patients treated with 2 mg/cm^2 achieved the primary endpoint (compared with 23.0% placebo); 53.3% of patients treated with ATX-101 1mg/cm^2 and 66.1% of patients treated with 2mg/cm^2 reached the objective on the SSRS (compared to 28.7 % placebo). Furthermore, submental fat caliper measurements showed a statistically significant reduction. Pain at the injection site was the common adverse effect in both groups, with others being variable, such as swelling, numbness, erythema, and bruising.

In phase III, double-blind trial by Ascher et al. (19) randomized 360 patients with submental fat (moderate to severe) to receive ATX-101 (1 or 2 mg/cm^2) or placebo injections for 4 sessions. The main objective was the same as the study by Rzany et al. (18). At 12 weeks, 58.3% of the patients treated with ATX-101 1 mg/cm^2 and 62.3% of the patients treated with 2 mg/cm^2 reached the target on the CR-SMFR scale (compared to the 34.5% of patients treated with placebo).

On the SSRS scale, 68.3% of patients treated with ATX-101 1 mg/cm^2 and 64.8% of 2 mg/cm^2 achieved the primary endpoint (compared with 29.3% of placebo). In the study of Rzany (2018) the measurement of the caliber of submental fat was not included. Adverse effects 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).

In the REFINE-2 trial (13), mandibular marginal nerve palsy occurred in 4.3% of patients treated with ATX-101 (compared with 0.8% of placebo), with recovery of 7 to 61 days. To prevent marginal injury to the mandibular nerve, it is recommended to avoid injections of ATX-101 over a line drawn 1.0-1.5 cm below the lower mandibular border. Another potential complication is injection volume-related dysphagia. In the REFINE-2 trial, this occurred in 2.3% of patients treated with ATX-101 (compared with 0.4% of placebo).

DISCUSSION

To date, there are several articles that have demonstrated the efficacy of non-surgical procedures to reduce submental fat deposits through the infiltration of substances with an adipocytolytic effect. Reeds et al. in 2013 (20) states that injections of phosphatidylcholine and deoxycholate can reduce the volume of abdominal fat and do not appear to increase inflammation markers or affect glucose and lipid metabolism. The main advantages of non-surgical fat reduction over the surgical technique are that it does not require anaesthesia or hospitalization, it is cheaper, it produces fewer scars and it is a simple and fast procedure (21). The ATX-101 was approved in 2015 as an

injectable drug for cosmetic purposes in the reduction of submental fat (13). The development of ATX-101 as a pharmacological treatment for fat reduction was based on the findings of Rotunda et al. (4), who demonstrated localized fat reduction using an injectable phosphatidylcholine formulation. From their study, DC was identified as the most active component responsible for the reduction of adipose tissue (4,22,23).

In clinical trials, the inflammatory response after DC infiltration (swelling, erythema, and bruising) has been shown to lead to repeated inflammation and thus potentially fibrosis (6,13,14). Therefore, it is recommended that ATX-101 be administered at 28-day intervals to allow resolution of the induced inflammation. Furthermore, injection into tissues other than adipose tissue can lead to tissue necrosis (4,5). In general, the side effects observed in clinical trials were mostly minor, of small intensity and duration, and resolved without sequelae (5,7,13). To minimize adverse effects, it is very important to use a strict ATX-101 injection protocol.

In conclusion, based on the bibliographic review, ATX-101 is the only drug currently authorized for the treatment of moderate to severe submental fat. This treatment offers an alternative to invasive measures such as liposuction, which presents a greater number of complications, requiring hospitalization and anaesthesia. These aspects of the liposuction turn out being unattractive for patients. Its use as an adipocytolytic agent is highly effective in reducing unwanted localized adiposities, demonstrating results from an objective point of view (use of submental circumference measurements and through the use of ultrasound), as well as from a subjective point of view from treated patients, using the SSRS scale.

Efficacy in the reduction of adipose tissue after the treatment with ATX-101 is maintained over time (more than 5 years after treatment), not requiring maintenance treatments to sustain the long-term effect or to reduce laxity of the skin. The main adverse effects of ATX 101 are mild and transitory, and usually localized at the injection site (pain, swelling, oedema, and bruising). They are more likely to appear in the first treatment sessions and decrease in the following sessions. Serious adverse effects are rare, including superficial skin ulceration and mandibular marginal nerve palsy, probably as a result of an inappropriate injection technique or a high dose. Therefore, to minimize the percentage of adverse effects, a good selection of patients, good technique performance and the administration of an adequate dose are important.

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