Research Article

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A Review on the Safety and Efficacy of ATX-101 in the Reduction of Submental Fat

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Abstract

Submental fullness, if associated with subcutaneous fat, can detract from an otherwise balanced and harmonious facial appearance - leading to an older and heavier look. According to a 2014 survey by the American Society for Dermatologic Surgery, approximately 7 out of 10 consumers are bothered by submental fullness. Traditional options for submental fullness include cervical rhytidectomy, liposuction and nonsurgical treatment strategies for SMF reduction such as mesotherapy; however, these methods are not without side effects and complications. ATX-101 is a first-in-class, injectable drug that has been developed for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF). Treatment with ATX-101 represents a nonsurgical, in-office procedure for reduction of SMF with no general anesthesia, and is a less invasive alternative to liposuction with or without neck lift. Across all studies, the efficacy results consistently demonstrate the superiority of ATX-101 relative to placebo in the reduction of SMF. The safety and tolerability of ATX-101 have been well characterized across a comprehensive development program and are acceptable. Therefore, given the overall balance of risks and benefits described, ATX-101 represents a safe, effective, and less invasive alternative to current treatment options for improvement in the appearance of moderate to severe convexity or fullness associated with SMF in adults.

Introduction

Facial aging often entails changes within the skin, facial skeleton, and soft tissue. It may be brought about by epidermal thinning, collagen loss and dermal elastosis over time. Facial fat is compartmentalized in a multidimensional trend on the midface [1].

The submental triangle, sometimes called suprahyoid triangle, is a division of the anterior triangle of the neck. The submental triangle is confined posterior (to the back) by means of the anterior belly of the digastricus, anterior (to the front) via the midline of the neck between the mandible and the hyoid bone and inferior (beneath) by the body of the hyoid bone while its floor is formed through the mylohyoideus [2]. Submental fullness, usually known as "double chin", is a common but undertreated facial problem. It may be influenced by several factors similar to aging, genetics and weight gain, and is usually resistant to weight loss programs and exercise alone [3].

Submental fat compartment plays an essential role in the appearance of the youthful and aesthetic neck, as well as the total attractiveness of the face. "Turkey gobbler" deformity within the submental area is often based on changes with the skin, fats, platysma, and underlying bone. Submental fat compartment is a discrete areolar chamber dwelling within the preplatysmal fat. Superficially, the compartment is bounded by the dermis, and its deep boundary is the platysma. The submental crease is created by the submental septum and creates the anterior or mesial border, and the distal or posterior border is shaped by the hyoid septum. The digastric septae forms the lateral borders of the compartment [4].

Submental fullness, if associated with subcutaneous fat, can detract from a balanced and harmonious facial look, thus leading to an older and heavier appearance. A 2014 survey by the American Society for Dermatologic Surgery has shown that roughly 7 out of 10 people are troubled by submental fullness. Submental fat is of certain concern for a lot of people. The presence of undesirable SMF, and related fullness/convexity of the submental region, can affect youthful look and the judgments of good looks from others. Excess SMF, which arise due to aging, habits, or genetic predisposition, is typically resistant to diet and exercise [4].

Usual choices for submental fullness include cervical rhytidectomy or necklift, liposuction with or without platysmaplasty and nonsurgical therapy strategies for SMF reduction like mesotherapy [4]. Cervical rhytidectomy or necklift is a surgical method that eliminates localized fat deposits underneath the chin, corrects muscle laxity, and tightens/removes sagging skin in this region. Medication may take weeks or months and may be drastically extended in certain participants like smokers and diabetics.

Potential complications include bleeding, contamination, nerve damage, scarring, risks associated with normal anesthesia, dyspigmentation, and death [5].

Liposuction (with or without platysmaplasty) is a choice for patients with adequate skin tone to permit subsequent epidermis contraction and adherence. Problems include contour irregularities (rippling and divots), adherence of the skin to underlying muscle, exposed platysmal bands, scarring, bruising, risks associated with anesthesia (if utilized), painful healing intervals, or loss of life. There is potential for scarring, bruising, and painful recovery periods, or surgical revision to achieve or maintain the preferred outcomes [5].

Mesotherapy has not undergone formal drug registration approaches, and neither efficacy nor safety has been centered in accurately controlled clinical studies. With regards to fat reduction, the ablative type of mesotherapy that leads to the destruction of fats cells is often performed with a combination of phosphatidylcholine (laptop) and deoxycholate (DC) or DC and different putative active ingredients. No drug product has been registered for the reduction of localized fat deposits in the USA [5]. Recently, there are studies concentrating on an injectable drug known as ATX-101 that has been used in the treatment of submental fullness.

The aim of this article is to discuss the safety and efficacy of ATX-101 as a treatment option for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF) in adults.

Background and Mechanism of Action

ATX-101 is a first-class injectable drug that has been developed for the improvement in the appearance of moderate to severe convexity or fullness related to submental fat (SMF). It is indicated for the improvement in the look of moderate to severe convexity or fullness associated with submental fat in adults [3]. ATX-101 is available as a sterile solution in single-use vials containing 2 ml of a 10 mg/ml (1% weight/quantity) solution in phosphate-buffered saline (PBS) with 0.9% benzyl alcohol (BA) as a preservative. It's administered in 0.2-mL injections spaced 1-cm apart into the subcutaneous (SC) fat using a 30 gauge (or smaller) 0.5-inch needle. The dosing regimen may result in an area-adjusted dose of 2 mg/cm2 and the highest intended dose in any individual treatment session is 100mg (ie, 10 ml). Treatments are given at intervals of not less than four weeks until the desired effect is attained, to a maximum of 6 treatment sessions [3].

The whole dose of ATX-101 given in every treatment session and the total quantity of treatments is tailored to the individual patient based on the quantity and distribution of SMF as well as the patient's desired outcomes. Desired results are gradual and mainly reached in fewer than 6 treatments (most patients improve in two to four treatments). Clinical studies have confirmed maintenance of effect for up to four years. In contrast to other aesthetic injectables (botulinum toxins or dermal fillers), retreatment with ATX-101 usually does not happen because its mechanism of action involves the destruction of fat cells. As a result, ATX-101 represents a major, nonsurgical remedy for the growing demand for SMF reduction and serves as a regulated replacement to unregulated, compounded, and misbranded lipolytic products with unknown quality, efficacy and safety [3].

As for its history and mechanism of motion, ATX-101 as deoxycholic acid, is a well-characterized endogenous secondary bile acid that serves to emulsify and solubilize dietary fats, thereby aiding in its breakdown and absorption within the intestine. It has been safely used as a solubilizing excipient for many years in globally accepted drug products, including the antifungal amphotericin B, and is also discovered in influenza vaccines wherein it is utilized to disrupt the virus throughout manufacturing [6].

Deoxycholic acid is the pharmacologically active constituent accountable for the reduction of localized subcutaneous (SC) fat. In vitro and in vivo trials have established that, when injected into SC fat, it disrupts the cell membrane of adipocytes causing adipocytolysis. Its activity is attenuated by protein, making its adipocytolytic result more potent in protein-negative tissues like SC fat as compared with regional protein-wealthy tissues similar to the skin, muscle, and blood vessels [6]. Additional nonclinical trials indicate that the local adipocytolysis brought about by DC elicits a predictable tissue response where macrophages are attracted to the region to do away with cell debris and lipids, which can then be cleared through natural processes. This is followed by the presence of fibroblasts and thickening of fibrous septa, suggesting an increase in the total collagen (ie, neocollagenesis). Exogenous DCA, administered as ATX-101, is indistinguishable from endogenous DCA and is regulated underneath the same homeostatic mechanisms. Removal from systemic circulation and the metabolic fate of DCA upon medication with ATX-101 are equal to endogenous DCA. ATX-101 is injected straight in SC fat tissue, acts locally to disrupt the adipocyte cell membrane, and consequently does not depend on systemic distribution to exert its adipocytolytic outcomes [6].

Following a single SC injection of ATX-101 at the maximum intended dose of 100 mg, the highest observed plasma DCA concentrations (mean C max) had been visible within 1 hour, indicating fast absorption and subsequent clearance from the systemic circulation. ATX-101 has low capabilities for cytochrome P450 (CYP) inhibition, CYP induction, and transporter inhibition. No medical drug-drug interaction reports had been warranted. Impact of other medicinal drugs is small [6].

When ATX-101 is injected into localized subcutaneous fat, DCA physically disrupts the cell membrane of adipocytes and creates adipocytolysis, the destruction of fat cells. The destruction of fat cells elicits a predictable tissue response wherein macrophages are attracted to the area to do away with cell debris and lipids that are then cleared via natural processes. There is the appearance of fibroblasts and observed thickening of fibrous septa suggesting an expansion in total collagen (ie, neocollagenesis). The activity of

DCA is attenuated by protein, making protein-negative tissues, such as SC fat, more inclined to its cytolytic effects. When injected into fat tissue, local protein-rich tissues such as skin and muscle are generally unaffected [6].

Histological changes are limited to subcutaneous fats. No changes were observed in the dermis or epidermis after medication. Instant focal adipocytolysis was noted, followed by the expected inflammatory tissue response. In Days 1-3 the inflammatory tissue response is particularly consisting of neutrophils. There is macrophage infiltration to do away with cellular particles and resolution of inflammation and thickening of the fibrous septae. For this reason ATX-101 dosing interval should not be less than four weeks.

Safety Results

Lipid and adipokine profiles following SC injection of ATX-101 into abdominal fat in healthy adults were evaluated. There was transient elevation of serum free fatty acids, which is within the range of DCA values discovered following a meal. Adipocytolysis triggered by ATX-101 did not lead to clinically significant effects or trends external of the normal range on serum lipids or adipokines. Lipid released from adipocytes after DCA treatment in rats was once proven to be processed by known lipid metabolism pathways. A study in rats confirmed slow absorption and tissue incorporation of metabolites; tissue distribution was predominantly to fat stores, principally to adipocytes at, and adjoining to, the site of injection. Majority were metabolized and utilized or excreted within 28 days after treatment. Two metabolites were detected in urine: suberic acid, an identified dicarboxylic acid metabolite of triolein, and an unidentified polar metabolite. Metabolites in plasma and feces had been under the detection limit and could not be identified [6].

Healing with ATX-101 was risk-free and well tolerated. Although some small variations in incidence of adverse events have been noted, the types, incidences, duration, and severity of adverse events were typically similar in spite of demographics or baseline traits. Adverse events associated with therapy had been stated in most patients in both medications and had been predominantly local reactions within the treatment area. AEs had been commonly transient and resolved within the treatment interval; 82% of AEs in the ATX-101 group and 89% of AEs in the placebo group resolved within 30 days [6].

Probably the most pronounced AEs in the pivotal studies have been local reactions on the injection site such as hematoma (predominantly pronounced as bruising), pain, anesthesia, edema, swelling, erythema, induration, paresthesia, nodule, and pruritus. These local reactions are anticipated based on the mode of administration (local injection), the pharmacologic action of ATX-101, and the resulting tissue response. To curb the potential for motor neuropraxia of the marginal mandibular nerve, injection above the inferior aspect of the mandible, or within the area defined by the 3-cm radius circle described above, is not advised [6].

Total incidence of treatment-associated skin ulcerations in patients treated with 2 mg/m2 ATX-101 was 0.5% (5/1050). No extreme skin ulceration events have been pronounced for either ATX-101 or placebo subjects throughout the clinical development program. The entire events had been stated as recovered/resolved. The few ulceration activities reported came about randomly with regards to therapy session. To decrease the potential for superficial skin ulceration, injection of ATX-101 must be delivered halfway into the SC fat layer and should not be continued for the duration of withdrawal of the syringe from the skin.

Within the pivotal studies, dysphagia was once stated in 10 subjects (1.9%; 10 events) in the ATX-101 group and 1 patient (0.2%; 1 occasion) in the placebo group. Most events had been slight. In summary, the events of dysphagia have been observed in a small proportion (1% to 2%) of subjects treated with ATX-101, were usually slight in severity, and mainly resolved within a number of days. Therapy with ATX-101 was no longer related to any clinically meaningful alterations in liver function tests, renal function assessments, serum lipid concentrations, or hematology results. ATX-101 had no influence on QT/QTc intervals, and no cardiac concerns had been recognized [6].

Despite the majority of subjects having reductions in SMF volume, greater than 90% of patients in the pivotal studies were suggested to have increased or unchanged skin laxity ratings at 12 weeks after final treatment, when compared with baseline, based on the Submental Skin Laxity Grade (SMSLG) scale. It could be concluded that the reductions in SMF due to ATX-101 don't lead to adverse influences on skin laxity [6].

Efficacy of ATX-101

Results from two equal, randomized, double-blind, placebo-controlled phase 3 reports carried out in the USA and Canada characterize the pivotal data that support the efficacy of ATX-101. Majority of patients mentioned improvements in the appearance of submental convexity/fullness and by measurements based on MRI [6]. The mentioned reductions in SMF are also related to the improvement in the impact of SMF on sufferer's self-perceptions and satisfaction. Decreases in SMF following treatment with ATX-101 had been visible in patients throughout studies, and in spite of baseline age, sex, race, and ethnicity, amount of SMF (moderate or severe), BMI, and skin laxity. Results of ATX-101 on the reduction of SMF are long lasting and have been maintained for up to 4 years following treatment [6].

ATX-101 is the potential first and only FDA-approved drug for submental contouring. It is clinically validated, with 18 SMF medical trials with larger than 2,600 subjects. It has significant, obvious results with a consistent efficacy and safety profile. It is corrective when you consider that it destroys fat locally and leaves surrounding tissues largely unaffected. About 87% of responders maintained response at 4 years. It is customized treatment because it is a type of non-surgical method tailored to attain a patient's favoured aesthetic outcome. Most patients observe improvement in 2 to 4 treatments [6]. The REFINE-1 and REFINE-2 pivotal trials met all primary and secondary endpoints. There is reduction

of submental fats as well as improvement in appearance and emotional outlook. There is submental volume reduction that is visible by MRI. There are no treatment-associated severe adverse events [6].

Conclusion

In summary, treatment with ATX-101 represents a nonsurgical, in-office procedure for reduction of SMF without general anesthesia, and is a less invasive alternative to liposuction with or without neck lift. Throughout all reviews, the efficacy outcomes consistently reveal the superiority of ATX-101 in relation to placebo in the reduction of SMF.

The efficacy of ATX-101 for improving the appearance of moderate to severe convexity or fullness related to SMF has been conclusively tested. The safety and tolerability of ATX-101 were characterized throughout a comprehensive development program and are appropriate. Thus, given the total balance of risks and advantages described, ATX-101 represents a dependable, safe, effective, and non-invasive replacement to current treatment options for the improvement in moderate to severe convexity or fullness associated with SMF in adults.

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