Alopecia after injection of ATX-101 for reduction of submental fat

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INTRODUCTION

Bile acids (BAs) are endogenously produced cholesterol derivatives that are found predominantly in bile and play a key role in lipid digestion. The surfactant activity of BAs is responsible for fat emulsification and subsequent solubilization, a process that is requisite for intestinal lipid absorption.[1] Deoxycholic acid (DCA), a secondary BA derived from cholic acid, has been used in a variety of medical applications.[1-3] Recently, DCA has been investigated in the cosmetic setting as a nonsurgical treatment of unwanted fat.[2,4] Initial therapeutic formulations were compounded mixtures of DCA and phosphatidylcholine, but none of these compounds received approval by the Food and Drug Administration (FDA).[5-7] In April of 2015, a synthetic proprietary formulation of DCA, ATX-101 (deoxycholic acid; Kythera Biopharmaceuticals, Inc, Westlake Village, CA [an affiliate of Allergan, plc, Dublin, Ireland]), became the first injectable DCA product to receive FDA approval for nonsurgical reduction of submental fat.[3,7,8]

Accumulation of preplatysmal subcutaneous fat under the chin can cause undesirable submental convexity and fullness, leading to loss of mandibular definition, as well as the impression of obesity or aging.[4,9] While liposuction and other surgical procedures are effective therapeutic options, they are invasive and carry significant risks to the patient, including extended recovery times, risk of infection, and scarring.[9,10] ATX-101 is commercially marketed in the United States as Kybella, which is a first-in-class injectable lipolytic therapy for the treatment of excess submental fat.[3,5,8] Therapy with ATX-101 represents a minimally invasive alternative to standard modalities that is both effective and safe. The most commonly reported adverse events associated with injection of ATX-101 include pain, erythema, edema, and bruising (Table I).[2-13] These events are generally mild to moderate in severity and transient.[2,4,7] To the best of our knowledge, of the reported associated side effects with ATX-101 injection therapy (Table I),[1-13] alopecia has not yet been published in the literature.

Abbreviations used:

BAs: Bile acids
DCA: deoxycholic acid
FDA: Food and Drug Administration

METHODS

A PubMed search wash conducted using various combinations of the following keywords: "Kybella," "ATX-101," "deoxycholic acid," "submental fat," "injection," "side effect," "adverse event," "alopecia," and "hair loss."

CASE

A 37-year-old white man sought evaluation and treatment for submental fullness. On exam, moderate submental convexity was observed, graded as a 2 on the Clinical-Reported Submental Fat Rating Scale.[2] Therapeutic options were discussed, and treatment with ATX-101 was recommended. The patient was in good health and had no history of

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Table I. Published adverse events of ATX-101 (deoxycholic acid) injection[1-13]

Location	Adverse events
Injection site	Alopecia (current report)
	Bleeding[5,7]
	Dysphagia[2,13]
	Edema[2-5,7-12]
	Erythema[2,3,5,7-10]
	Hematoma (including bruising)[2-5,7-13]
	Hyperhydrosis[9]
	Induration[2,4,7,8,10,11]
	Marginal mandibular nerve injury[2,4,11,13]
	Nodule[2]
	Numbness[2-5,7-9,11]
	Pain[1-4,6-11]
	Pallor[9]
	Pruritus[2,5]
	Tightness[5]
	Warmth[9]
Noninjection site	Headache[2]
	Nasopharyngitis[2]
	Tremor[9]

alopecia areata, atopic dermatitis, or any skin or connective tissue disease.

The initial treatment consisted of 21 discrete injections into the submental region at 1 cm^2 intervals, with 2 mg of DCA delivered uniformly and deeply at about a 2/3—needle depth with a 30 gauge ½—inch needle into the subcutaneous fat per injection (Fig 1). The patient tolerated the procedure without difficulty. However, when he returned for a 1-month follow-up evaluation, examination revealed patchy areas of alopecia affecting the patient's beard in the submental area, corresponding to his previous treatment sites (Fig 2). Repeat treatment was deferred. At this point, the authors believed that alopecia would be a transient adverse event, and the patient preferred to avoid intralesional injections, a biopsy, or minoxidil use. The patient was given free samples of 0.03% bimatoprost (Latisse, Allergan, Irvine, CA) solution daily to the affected area. Eleven months after his initial treatment with ATX-101, the patient still had persistent areas of alopecia in most of the treated areas with some new hair growth at the periphery (Fig 3).

DISCUSSION

The soft tissue composition of an individual's face and neck significantly impacts appearance and self-perception. The accumulation of fat in the preplatysmal submental compartment can cause an unwanted aged or overweight appearance.[11] The degree of submental fullness is thought to be caused by a combination of factors, including genetic predisposition, aging, and diet.[2,7,11] ATX-101 is the first injectable lipolytic therapy FDA-approved for improving the appearance of convexity or fullness of the submental area by reducing and contouring subcutaneous fat.[2,3,9,13]

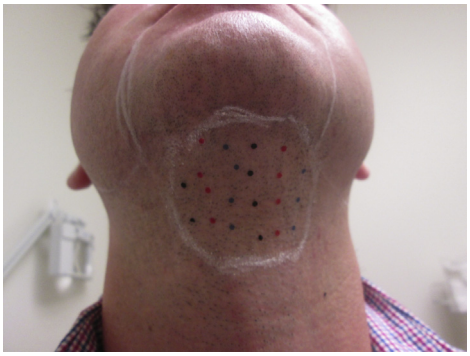

Fig 1. Patient before treatment with ATX-101.

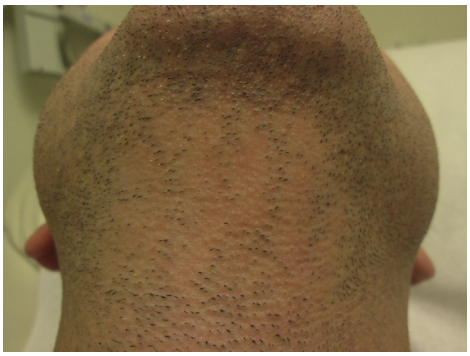

Fig 2. Patient 1-month posttreatment with ATX-101.

DCA and bile acids in general are essential to numerous biologic processes, the most important of which involves the metabolism and absorption of dietary lipids.[1,2] In its injectable form, ATX-101 induces cellular membrane disruption via pore formation, resulting in focal adipocyte lysis.[1,2,5,13] It also induces a local inflammatory response that results in recruitment of macrophages and fibroblasts, with subsequent stimulation of collagen production.[2-4,7,13] The mechanism of skin retraction occurring with fat reduction is incompletely understood but might be caused by the replacement of injured adipose tissue with fibrosis.[5] Importantly, this cytolytic activity is attenuated by albumin and tissue-associated protein.[9,11] Thus, nearby protein-rich tissues such as skin, vasculature, and muscle are unaffected by subcutaneous adipose injections.[7,9]

A number of clinical studies have demonstrated statistically significant patient satisfaction with the

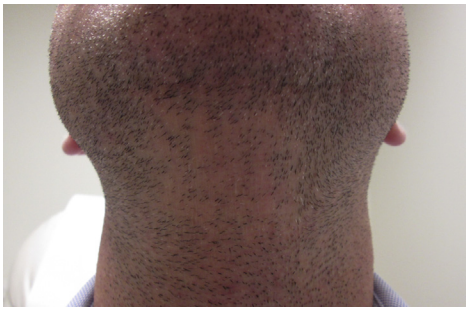

Fig 3. Patient 11 months posttreatment with ATX-101.

appearance of submental fullness after injectable lipolytic therapy.[4-6] In addition to patient satisfaction, injectable DCA therapy is minimally invasive and thus associated with fewer complications and less recovery when compared to more invasive procedures.[2,4,7,9] While the treatment with ATX-101 is generally well-tolerated, therapy has been associated with a number of adverse events (Table I).[2,7] Overall, reported side effects with ATX-101 in clinical trials were typically mild to moderate, transient, and localized to the injection site.[4,7,10,11] The most commonly reported events were minor and included pain, edema, erythema, and bruising; and notably, these events frequently occurred in the placebo groups as well.[2-13] This was not surprising because the aforementioned adverse events are the most common and expected effects associated with all injection-based procedures.[3,4,11] Rarely, induration, dysphagia, hyperhidrosis, marginal mandibular nerve injury, nodule formation, paresthesia, pallor, pruritus, tenderness, and warmth have been reported to occur.[2-6,9-11,13] Most side effects resolved within days, and nearly all patients experienced complete resolution before follow-up at 1 month.[2,7,9-11] In addition, median duration of any recurrent symptoms was also observed to be shortened with subsequent treatments.[2,4]

CONCLUSION

To the authors' knowledge, this is the first published case of localized alopecia associated with subcutaneous injection of AXT-101 for the treatment of submental fat. Moreover, in contrast to the transient nature seen with other reported adverse events, the hair loss in this patient has been persistent and refractory to treatment with topical bimatoprost. The alopecia appeared diffusely at onset and seemed to affect most, if not all injection sites. Some peripheral injections sites have had some modest recovery of hair growth. Similar depth and volume of products were used at each site, and the baseline hair density was similar, perhaps there was variability in the amount of subcutaneous fat, and the persistent sites had less subcutaneous fat, allowing more exposure of peri-bulbar fat to the ATX-101.

The mechanism of alopecia development in this patient remains unclear, and further characterization is limited by the lack of additional cases in the literature. Similar to any novel therapeutic, postmarketing surveillance data will allow for a more comprehensive description of side effects associated with AXT-101 therapy.

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