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Submental Area Treatment with ATX-101: Relationship of Mechanism of Action, Tissue Response, and Efficacy

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Background: ATX-101 is an injectable, synthetically derived formulation of deoxycholic acid used for submental fat reduction.
Methods: A narrative review of references relevant to the mechanism of action of ATX-101 and its relationship to efficacy and inflammatory adverse events was conducted.
Results: When injected into subcutaneous fat, deoxycholic acid physically disrupts adipocyte cell membranes, leading to local adipocytolysis, cell death, and a mild, local inflammatory reaction consisting of macrophage infiltration and fibroblast recruitment. At Day 28 postinjection, inflammation largely resolves, and key histologic features include fibrotic septal thickening, neovascularization, and atrophy of fat lobules. Based on the mechanism of action of ATX-101 and the demonstrated inflammatory response, localized inflammation and swelling are expected following treatment. Indeed, postinjection swelling and other local injection-site events, including pain, erythema, and bruising, are common during and after treatment. Because of inflammatory sequelae following injection, reduction in submental fat is gradual and may require months before the full response is apparent. Patients may also require multiple treatment sessions to achieve their treatment goals. Repeated treatments may result in less pain and swelling over time owing to a combination of factors, including less target tissue allowing for lower doses/injection volumes, persistent numbness, and greater tissue integrity from thickened fibrous septa.
Conclusions: Physicians can manage expectations by counseling patients that, based on the mechanism of action of ATX-101 and data from pivotal clinical trials, ATX-101 treatment results in localized inflammation/swelling and gradual submental fat reduction. Patient education about common local adverse events is critical.
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INTRODUCTION

Submental fat can produce an unattractive fullness below the chin and adversely affect an individual's facial appearance and psychological well-being.[1] Unwanted submental fat is common, as indicated by a 2018 survey by the American Society for Dermatologic Surgery, in which 73% of respondents indicated being most bothered by excess fat under the chin or neck.[2] Until recently, the only options for reducing submental fat were surgical procedures such as liposuction.[3,4]

ATX-101 (Kybella; Allergan USA, Inc., Irvine, Calif.; Belkyra, Allergan plc, Dublin, Ireland) is a synthetically derived formulation of deoxycholic acid, in injectable form, that was approved in the United States (Kybella) in 2015 to treat the appearance of moderate to severe

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convexity or fullness associated with submental fat in adults[5,6] and is also approved and marketed in Canada, Australia, Europe, and South Korea (Belkyra).[5–10] Multiple treatment sessions spaced at least 4–6 weeks apart are recommended to achieve patient goals.[6] In clinical trials, treatment with ATX-101 produced significant improvement in submental fat from both patient and physician perspectives.[11,12] The most common adverse events (AEs) following ATX-101 treatment were injection-site events, including local swelling, bruising, numbness, erythema, and pain.

Postinjection swelling has been identified as a potential barrier to use of ATX-101 for submental fat reduction.[13] Understanding how injection-site swelling and other correlates of local inflammation relate to the mechanism of action (MOA) of ATX-101 may enable clinicians to better manage patient expectations following treatment. In this narrative review of the relevant literature, we discuss how the MOA of ATX-101 relates to efficacy and inflammatory AEs. We examine how the MOA of ATX-101 causes a predictable tissue response in the submentum characterized by swelling and discuss implications for treatment paradigms. We additionally describe management of local AEs related to inflammation.

Takeaways

Question: How does the mechanism of ATX-101 relate to tissue responses, efficacy, and inflammatory adverse events?

Findings: Physical disruption of adipocyte cell membranes by ATX-101 results in gradual submental fat reduction and a mild, local inflammatory reaction, which may lead to local injection-site events.

Meaning: Knowledge of the mechanism of ATX-101 may help clinicians to better manage patient expectations and local adverse events following treatment and provide appropriate patient education about common adverse events and expected recovery times.

MECHANISM OF ACTION OF ATX-101

Deoxycholic acid is a biliary acid produced in the intestinal tract during digestion.[14,15] It emulsifies and solubilizes intraintestinal dietary fats to prepare them for enzymatic degradation and absorption.[14] When injected subcutaneously, it physically disrupts adipocyte cell membranes, leading to local adipocytolysis and subsequent cell death.[16,17] Its selectivity for fat cells may result from the neutralizing effects of albumin and tissue-associated proteins, which attenuate the cytolytic activity of deoxycholic acid, thereby protecting nonadipose cells.[18,19] Adipocytolysis predictably elicits a mild, local, and transient inflammatory response, with macrophage infiltration diminishing over time as fibroblasts and fibrosis predominate.[18,20]

Histologic evidence supports these findings. Changes in inflammation were evaluated following injections of ATX-101 into abdominal fat of adults (Fig. 1).[21] On day 1 postinjection, key histologic features included adipocytolysis, blood vessel injury, hemorrhage, and neutrophilic inflammation. Inflammation on day 3 was less dense relative to day 1. Seven days postinjection, inflammation was mild and more lymphomononuclear, with the most prominent feature being adipocytolysis. Lipid-laden macrophages were noted in the fat septa, and repair of vascular injury (eg, intimal thickening, recanalized thrombi) was evident in day 7 samples. By day 28, inflammation had largely resolved (primarily septal), and key histologic features included fibrotic septal thickening, neovascularization, and atrophy of fat lobules.

The proposed mechanism of action of ATX-101 is shown in Figure 2. Injection of ATX-101 results in adipocytolysis, which elicits a local tissue response consisting of macrophage infiltration and fibroblast recruitment.[5,21,22] Histologic changes are limited to the subcutaneous fat and do not affect the dermis or epidermis.[21] Although blood vessel injury was observed, evidence of vascular repair was detected in histologic specimens 1 week after injection. Based on the evidence of neovascularization and fibroblast recruitment, ATX-101 may induce neocollagenesis, facilitating submental skin retraction as submental fat diminishes over time.[21]

CLINICAL EFFICACY OF ATX-101

Four phase-3 clinical trials evaluated the efficacy and safety of ATX-101 for the treatment of submental fat: two identical, randomized, placebo-controlled trials conducted in North America[11,12] and two identical, randomized, double-blind, placebo-controlled trials performed in Europe.[11,23,24] Adults in the North American studies received up to six treatment sessions with ATX-101 (2 mg/cm^2) or placebo, spaced approximately 28 days apart.[12] Adults in the European studies received ATX-101 (1 or 2 mg/cm^2) or placebo in up to four treatment sessions, each separated by approximately 28 days.[11] All four trials evaluated the efficacy of ATX-101 12 weeks after the last treatment session.[11,12]

Figure 3A shows that, in a pooled analysis of the North American trials, significantly ($P < 0.001$) greater proportions of patients treated with ATX-101 versus placebo had improvement of one grade or more from baseline on the Clinician-Reported Submental Fat Rating Scale (CR-SMFRS), Patient-Reported Submental Fat Rating Scale (PR-SMFRS), or both scales (composite score, the coprimary efficacy endpoint).[12] These scales rate submental fat from 0 (absent/no chin fat) to 4 (extreme/a very large amount of chin fat).[11,12] A survey of 385 patients supports the validity of a one-grade improvement on the CR-SMFRS as a meaningful clinical endpoint.[13]

Figure 3B shows the proportion of CR-SMFRS treatment responders 12 weeks posttreatment in a pooled analysis of the European studies.[11] The proportion of CR-SMFRS responders was significantly higher in the ATX-101 (1 or 2 mg/cm^2) group than in the placebo group (both $P < 0.001$). Response was also evaluated after each treatment session. The proportion of responders increased over the study course and was significantly greater with ATX-101 than placebo after the third treatment.

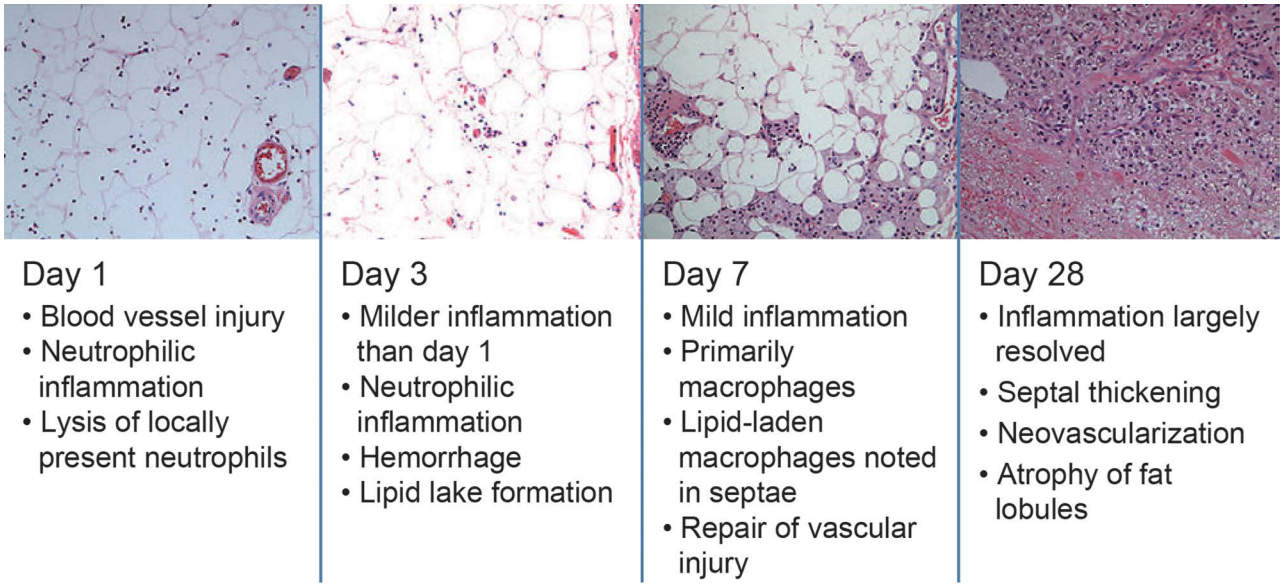

Fig. 1. Histologic changes in inflammation following ATX-101 injection. Reprinted with permission from Wolters Kluwer Health from *Dermatol Surg*. 2020;46:70–77.[21]

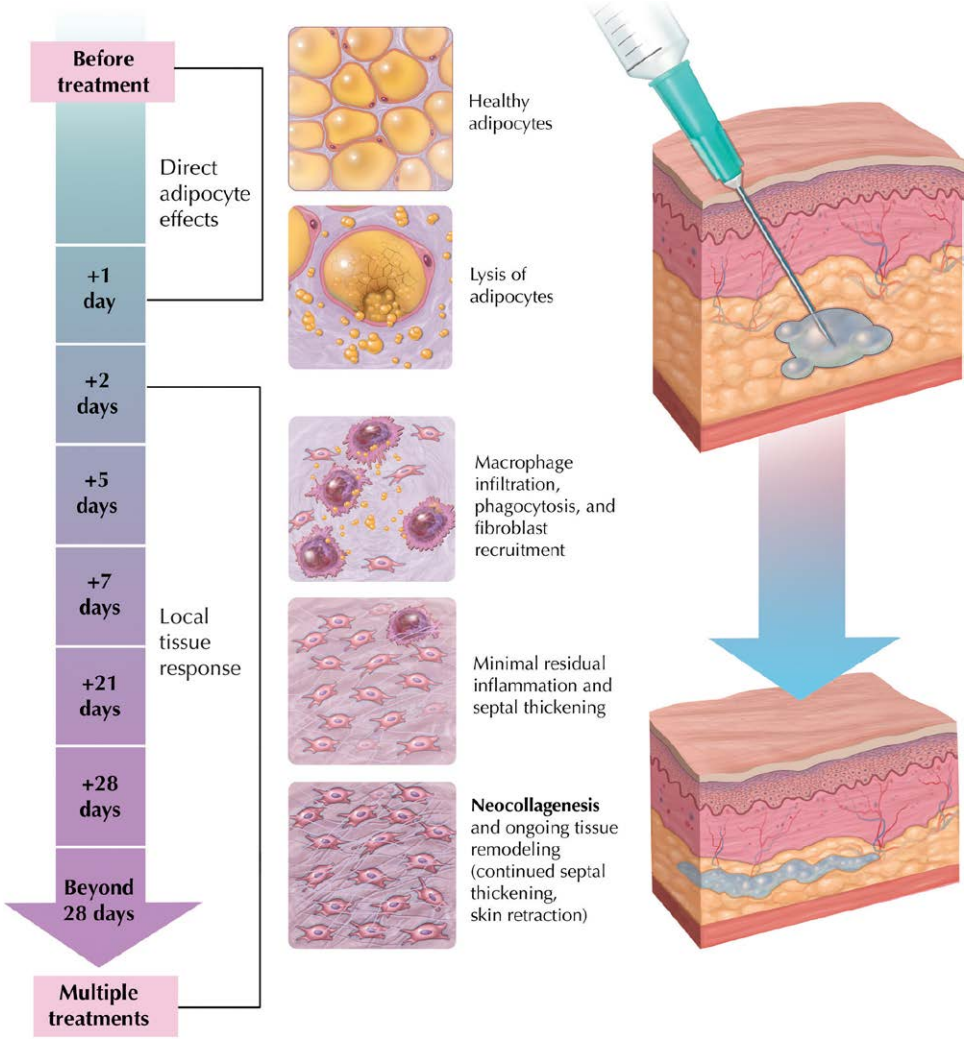

Fig. 2. Mechanism of action of deoxycholic acid (ATX-101).[5,21,22]

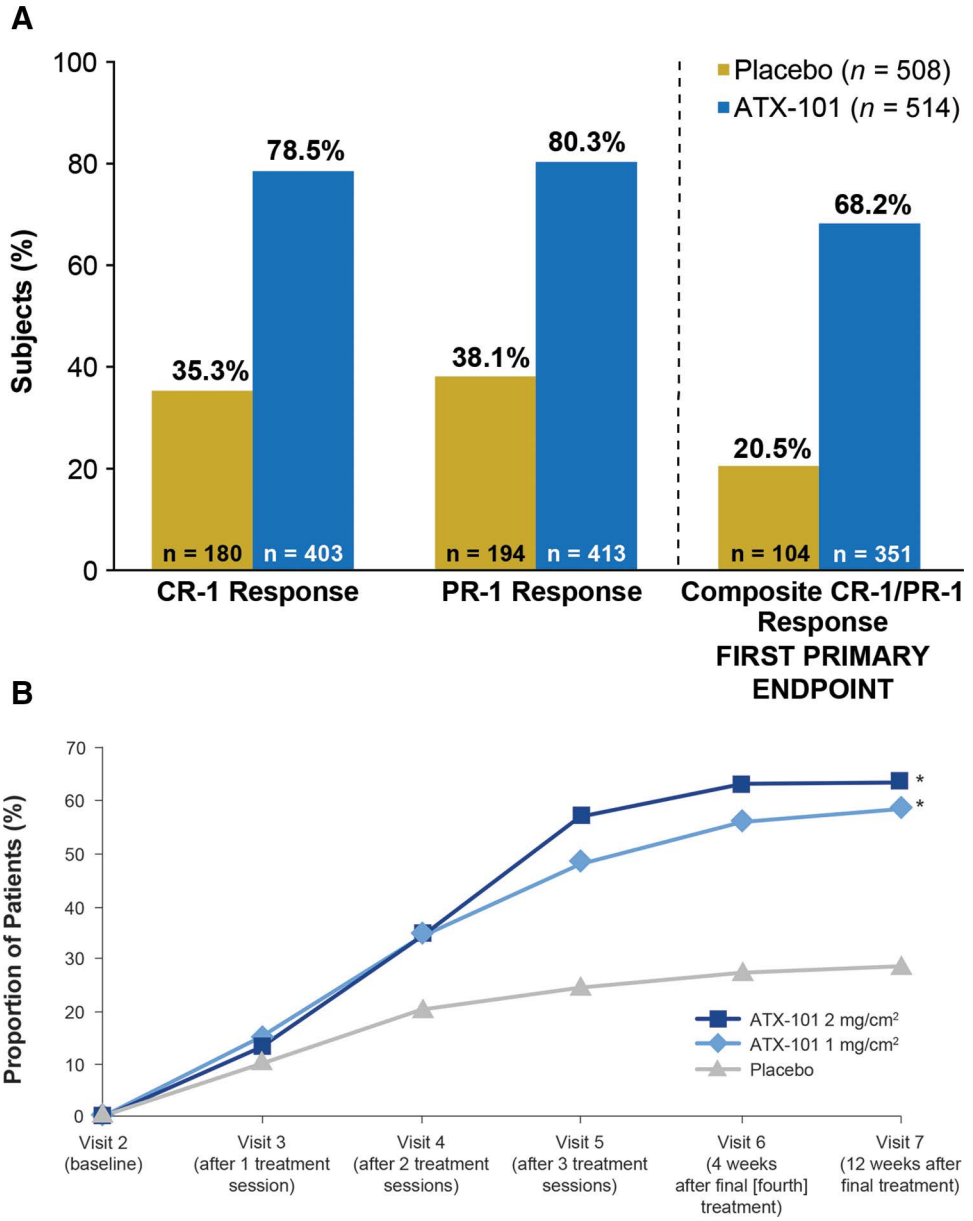

Fig. 3. Efficacy of ATX-101 at 12 weeks after last treatment in the North American phase-3 clinical trials. A, Percentage of patients achieving at least 1-grade improvement in submental fat from baseline at 12 weeks after last treatment based on CR-SMFRS (CR-1 response), PR-SMFRS (PR-1 response), and composite CR-1/PR-1 response. $P < 0.001$ for all comparisons between ATX-101 and placebo. Reprinted with permission from *Aesthet Surg J*. 2018;38:998–1010.[12] B, Studies 16 and 17: Proportion of treatment responders (≥1-grade reduction on the CR-SMFRS) from visit 2 (baseline) to the final follow-up visit (12 weeks after the final treatment). *$P < 0.001$ vs placebo. Reprinted with permission from *Aesthetic Plast Surg*. 2014;38:849–860.[11] CR, Clinician-Reported; CR-SMFRS, Clinician-Reported Submental Fat Rating Scale; PR, Patient-Reported; PR-SMFRS, Patient-Reported Submental Fat Rating Scale.

A meta-analysis of the four phase-3 trials found no statistically significant differences between 1-mg per cm^2 and 2-mg per cm^2 doses with regard to CR-SMFRS or PR-SMFRS response.[25] No significant differences between the two dose groups were observed in the frequency of any local AE with the exception of induration, including fibrosis (23.5% versus 16.0%, $P = 0.04$).

A post hoc analysis of data from a phase-3b, randomized, placebo-controlled exploratory study designed to evaluate the effectiveness of various interventions for managing AEs from a single ATX-101 treatment found that submental appearance continues to improve for at least 2–3 months posttreatment.[22] Similarly, a single-center retrospective analysis of medical records of 202 adults

treated with ATX-101 found that clinically meaningful improvement continued for several months after treatment in some patients.[26] These findings imply that the injection protocol should be modified by lengthening the gap between treatments and waiting for a maximum response before injecting repeat doses.

LOCAL ADVERSE EVENTS ASSOCIATED WITH ATX-101: FOCUS ON INFLAMMATION

Local injection-site events (including swelling, pain, erythema, and bruising) are common during and shortly after ATX-101 treatment, and are generally mild to moderate in severity.[19,27] The degree to which patients are affected by such AEs can vary considerably, but fewer injection points and lower injection volumes may reduce AE incidence.[28]

LOCAL ADVERSE EVENTS IN PHASE-3 CLINICAL TRIALS

Spontaneous reports of AEs were collected throughout the North American phase-3 clinical trials[11,12]; AEs were recorded at each study visit and at approximately 7 days following each treatment in the European studies.[11,23,24]

The incidence of common, treatment-related injection-site AEs from the pooled analysis of the North American and European phase-3 study populations is summarized in Tables 1[12] and 2,[11] respectively. In the North American studies, median duration of edema/swelling in the ATX-101 treatment groups was 10–11 days compared with 4 days in the placebo group (Table 1).[12] Compared with edema/swelling, lower median durations were observed for bruising, pain, and erythema following ATX-101 treatment. A post hoc analysis of pooled data from the North American studies found that the incidence and severity of edema/swelling (Fig. 4),[12] pain, and hematoma (ie, bruising) were highest during the first session and steadily declined over subsequent sessions, likely related to fewer injection points and lower injection volumes used in each subsequent treatment. Similarly, the median duration of injection-site AEs in the European studies was longer after the first session (6–7 days) than after subsequent treatment sessions (3–4 days).[11] Consistent with these observations, an open-label, phase-3b trial of ATX-101 in 165 adults with moderate-to-extreme submental fat found that the frequency and duration of downtime were greatest following the initial treatment session and decreased with subsequent sessions.[29]

Table 1. Incidence and Median Duration of Common Injection-site Adverse Events from a Pooled Analysis of the Two North American Studies*

	Pooled North American Study Population			
	Placebo (n = 504)		ATX-101 (n = 515)	
Injection-site Adverse Events	Patients (%)	Median Days	Patients (%)	Median Days
Hematoma (bruising)	70.0	9	71.5	9
Pain	31.3	3	69.5	7
Anesthesia (numbness)	5.8	2	66.2	43
Edema	29.2	4	60.4	10
Swelling	15.7	4	33.2	11
Erythema	17.9	2	26.6	3
Induration	2.6	6	23.3	28
Paresthesia	3.8	2	13.8	10
Nodule	2.6	5	13.4	23
Pruritus	6.0	3	12.4	7

*Adapted from *Aesthet Surg J.* 2018;38:998–1010.[12]

Table 2. Incidence of Common Injection-site Adverse Events Considered to Be Treatment Related from the Pooled European Study Population*

	Pooled European Study Population			
		ATX-101		
Patients, %	Placebo (n = 236)	1 mg/cm² (n = 237)	2 mg/cm² (n = 243)	Total (n = 480)
Pain including burning	27.5	84.0	85.2	84.6
Swelling including edema	26.3	60.8	60.5	60.6
Bruising including bleeding	45.3	57.8	53.4	56.0
Numbness	2.1	46.0	51.9	49.0
Erythema	22.5	40.5	40.0	40.2
Induration including fibrosis	1.7	16.9	23.0	20.0

*Adapted from *Aesthetic Plast Surg.* 2014;38:849–860.[11]

PRACTICE PATTERNS AND LOCAL ADVERSE EVENTS IN THE CLINICAL PRACTICE SETTING

Observational data can provide a perspective of real-life practice patterns as well as important information about treatment safety and tolerability in the clinical practice setting. Humphrey and colleagues[26] conducted a single-center retrospective review of medical records from 202 adults who received up to nine treatment sessions (mean, 1.7 sessions) with ATX-101. Patients received slightly lower volumes of ATX-101 than those given in the North American studies (median, 4.6 mL versus 5.2 mL), with a longer interval between the first and second treatments (mean, 99 days). All patients experienced discomfort/pain and some degree of swelling.

THE LINKS BETWEEN MECHANISM OF ACTION, INJECTION-SITE INFLAMMATION, AND CLINICAL EFFICACY

Figure 5 summarizes the relationship of the MOA of ATX-101, the development of injection-site inflammation, and clinical efficacy.[5,21,22,26,28,30–32] As described earlier, injection of ATX-101 results in adipocytolysis, with destroyed adipocytes no longer able to store or accumulate fat.[16,17,31] Adipocytolysis and the release of cell contents and membrane fragments elicit a mild, local inflammatory response, resulting in neutrophilic inflammation and attracting macrophages.[18,20,21] Local swelling and irritation likely result from adipocytolysis, inflammation, and temporary vascular injury (also observed at day 1); leakage from damaged vessels may also contribute to bruising.[21] Natural processes eliminate cellular debris and free lipids, and by day 7, inflammation is mild, lipid-laden macrophages are evident, and there are signs of vascular repair.[18,20,21] Swelling, bruising, and pain have thereby greatly diminished or resolved by this point.[12,30]

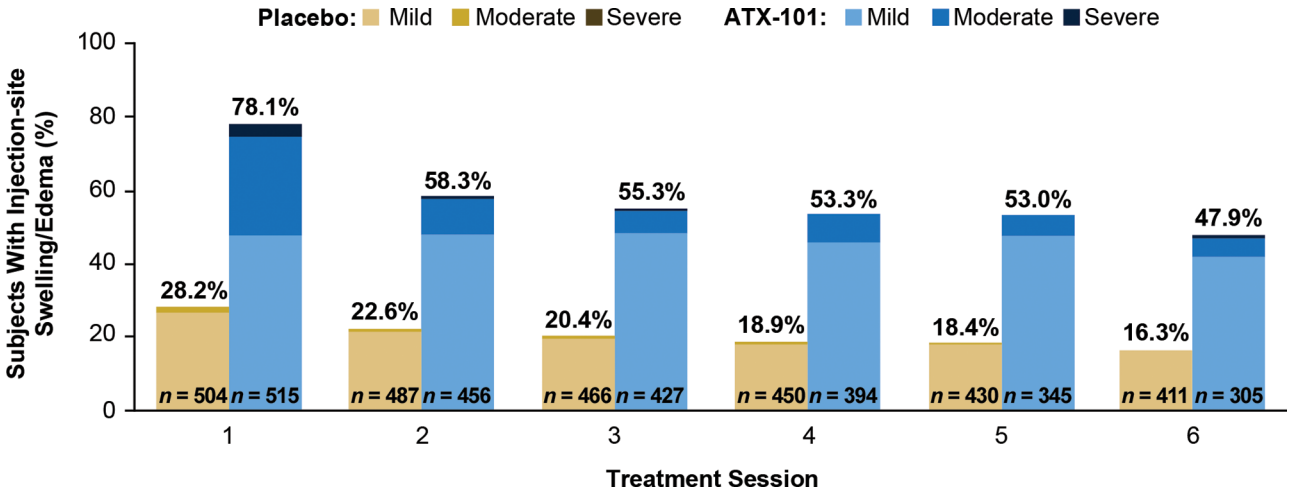

Fig. 4. Incidence and severity of injection-site adverse events decline over subsequent treatment sessions. Adapted with permission from *Aesthet Surg J*. 2018;38:998–1010.[12] © 2018 The American Society for Aesthetic Plastic Surgery, Inc. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

By day 28, inflammation has largely resolved (limited to septa) and fat lobules have atrophied.[21] At this point, many patients will experience an improvement in submental appearance, although caliper-measured submental fat thickness may be increased due to residual induration.[22] Caliper measurements, however, are a crude objective assessment of fat thickness used in clinical trials and are limited in their utility for confirming reduction of submental fat volume in clinical practice.[25,33] Gradual improvement in submental fat may continue beyond 28 days. Representative patient images at screening and week 32 illustrate this point. [**See figure, Supplemental Digital Content 1,** which displays the representative patient images at screening (top and bottom left images) and at week 32 (top and bottom right images). **http://links.lww.com/PRSGO/B993**.]

It has been hypothesized that, following submental ATX-101–induced adipocytolysis and subsequent inflammation, tissue remodeling and neocollagenesis may occur over several months.[22] High-resolution ultrasonography, magnetic resonance imaging, and three-dimensional photographic imaging[34–36] before the injection and on follow-up may prove helpful in objectively assessing the effect of ATX-101 by demonstrating the decrease in fat thickness as well as volume reduction. Accordingly, a prospective evaluation of 13 patients undergoing treatment with ATX-101, in which objective data were obtained using 3D photographs and corresponding volumetric change calculations, demonstrated a statistically significant increase in submental volume during the immediate recovery period (24–48 hours postinjection) followed by a significant decrease in submental volume measured 3 months after each injection.[34] Patients who underwent more than three treatment sessions achieved, on average, 92.8% of the total volume reduction after the initial three sessions.

Depending on the patient's baseline level of submental fat and individual treatment goals, multiple treatment sessions may be required. Repeated treatments result in less pain and swelling over time, likely due to less target tissue, allowing for lower doses/injection volumes, persistent numbness, and thickened fibrous septa,[37] which may contribute to greater tissue integrity. Additional treatments cause adipocytolysis of remaining submental fat and result in gradual subcutaneous tissue reduction.

MANAGEMENT OF LOCAL ADVERSE EVENTS

Considering the individual needs and circumstances of each patient is an important strategy for optimizing patient outcomes and mitigating AEs. This may also improve patient comfort and willingness to undergo additional treatment sessions. Because there is wide variation in the degree of swelling, pain, and bruising that patients experience during and following ATX-101 injection, an individualized approach is needed.[28] Figure 6 demonstrates examples of mild and moderate swelling at various postinjection time points.

A double-blind, placebo-controlled, exploratory study evaluated various management paradigms for common injection-site AEs (swelling/edema, pain, and bruising) after a single treatment session with ATX-101.[30] Patients were randomly assigned to one of four interventions: (1) cold, (2) cold/lidocaine, (3) cold/lidocaine/loratadine/ibuprofen, and (4) cold/lidocaine/loratadine/ibuprofen/chin strap (Table 3).[30] In addition to spontaneous AE reports, swelling/edema and bruising were graded by the investigator on a scale from 0 (absent) to 4 (affecting the face/neck beyond the treatment area) immediately pretreatment, at 4 hours posttreatment, and on days 1, 2, 3, 7, 14, 21, 28, and 84 posttreatment. Patients rated pain level using a visual analog scale and pain quality using the Short-Form McGill Pain Questionnaire.

Pain was generally mild, peaked within 1–5 minutes, was substantially reduced within 15 minutes, and resolved within 3 hours following treatment with ATX-101.[30] Compared with use of a cold pack alone, the addition of topical lidocaine/injectable lidocaine with epinephrine

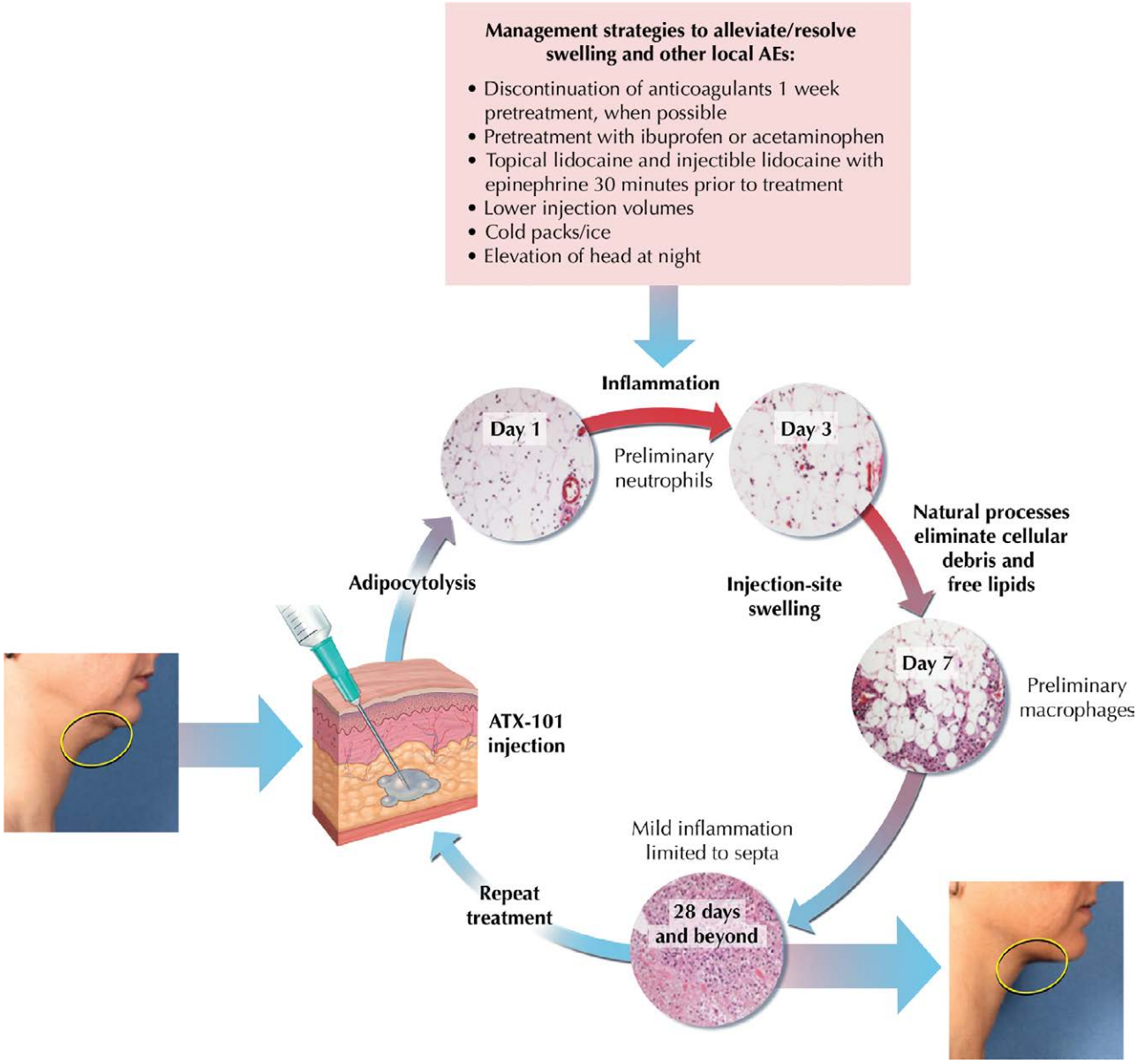

Fig. 5. Relationship of mechanism of action, injection-site swelling, and clinical efficacy.[5,21,22,26,28,30–32]

reduced median peak pain by 17%. A 40% reduction in pain was achieved when ibuprofen and loratadine were added. However, use of a chin strap did not further reduce pain. Peak swelling was modest and occurred on day 1, and, although minimal after day 7, was greater versus placebo until around day 28. Use of ibuprofen, loratadine, or a chin strap, however, did not substantially reduce swelling compared with cold application alone. Bruising was confined to the treatment area, peaked on day 1, and was greatly diminished by day 14. Injectable lidocaine with epinephrine slightly reduced bruising compared with cold alone, likely due to epinephrine-medicated vasoconstriction.

Management strategies based on the experience of clinicians who use ATX-101 extensively in clinical practice are generally consistent with the study findings described above.[28,38] Accordingly, treatment with acetaminophen or ibuprofen given up to an hour before treatment (and following treatment) is recommended to reduce pain. Discontinuation of oral drugs with known anticoagulant effects up to 10 days before treatment should be considered, when possible, to decrease bruising. Additionally, as suggested by Fagien and colleagues, pretreatment injection of 1%–2% lidocaine with epinephrine can minimize bruising.[28] Premixing ATX-101 with 2% lidocaine has also been shown to reduce injection-related pain.[39,40] The effect of premixed lidocaine on the efficacy of ATX-101 has not been studied in well-controlled trials. Application of a topical anesthetic cream may reduce the pain of needle penetration as well as provide confidence to the patient that he or she is anesthetized before the procedure.

Fig. 6. Patient images showing grades 2 and 3 swelling at Days 0, 1, 7, and 28 following injection of ATX-101. Images courtesy of Allergan Aesthetics, an AbbVie Company.

Careful injection technique,[41] which requires knowledge of relevant anatomy,[42,43] and pretreatment and immediate posttreatment cooling with ice or a Zimmer chiller device are recommended to reduce swelling.[28,31,42] Patients should also be advised to apply ice for 1 hour after they leave the office and to sleep with their head elevated for several nights. Per the study by Fagien and colleagues,[28] continuous compression does not substantially improve swelling. Additionally, to enhance precision of injection and volume determination, as a clinician is gaining experience with using ATX-101, it may be helpful to carefully mark the area to be injected with injection points and calculate the optimal dose.

Patients may prefer to schedule treatment during colder months, when they can use clothing to cover up any swelling or redness, and at a time when they are free of social obligations for the following several days.[28,44] Because the majority of edema tends to resolve within 72 hours, patients may also choose to schedule treatment on a Friday so that they can expect to return to work the following Monday without needing to conceal the treatment area.[34] Setting patient expectations by informing them that local injection-site reactions, such as swelling, tend to be less severe and of shorter duration with subsequent treatments may also alleviate anxiety about future treatments.[12]

Table 3. Management Paradigms Targeting Common Injection-site Adverse Events[30]

Paradigm 1	Paradigm 2	Paradigm 3	Paradigm 4
Cold*	Cold* Lidocaine + epinephrine†	Cold* Lidocaine + epinephrine† Loratadine‡ Ibuprofen§	Cold* Lidocaine + epinephrine† Loratadine‡ Ibuprofen§ Chin strap¶

*Application of a chemical cold pack to the treatment area for 10 minutes before treatment and 15 minutes after treatment.
†Application of 4% topical lidocaine cream across the treatment area 45 minutes before treatment, followed by injections of 1% lidocaine with epinephrine within the submental area 25 minutes before treatment.
‡Loratadine 10 mg per day for 7 days before and 7 days after treatment.
§Ibuprofen 600 mg at least 1 h before treatment and three times per day for 3 days after treatment and then as needed until 7 days after treatment.
¶Chin strap applied approximately 15 minutes after treatment for at least 24 hours and continued up to day 3 (removed only for study procedures and showering) based on the investigator's discretion.

CONCLUSIONS

Although, as a review article, this article is limited to discussing existing controlled prospective data from the peer-reviewed literature along with information gleaned from clinical practice, the guidance provided herein may enable clinicians to better manage patient expectations and local AEs following ATX-101 treatment. Physicians should manage patient expectations by counseling patients that, based on the MOA of deoxycholic acid and data from ATX-101 pivotal clinical trials, ATX-101 treatment results in localized inflammation/swelling and gradual submental fat reduction.[11,12,41] It is important that clinicians educate patients about common local AEs, such as bruising, numbness, pain, and swelling, and their expected recovery times.[41] An individualized injection approach, based on patient-specific needs, is an effective strategy to mitigate and alleviate swelling and other local AEs following ATX-101 injection.[28]

Use of lower injection volumes than those used in clinical trials has been described in clinical practice settings.[26,32,44] Although this approach may potentially result in decreased severity and duration of swelling and other local injection-site events, lower injection volumes are likely to result in less improvement in submental fat with each session and may negatively affect patient satisfaction with treatment. The optimal interval between treatment sessions has yet to be determined, but a longer treatment interval has been suggested, allowing for complete resolution of inflammation, maximal treatment effect, and potentially fewer sessions to achieve aesthetic success.[22] This strategy may also result in fewer, less severe injection-site AEs if lower injection volumes of ATX-101 are subsequently needed.

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