International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	INTRADERMAL BOTULINUM TOXIN FOR ERYTHEMATOTELANGIECTATIC ROSACEA: MECHANISMS, DOSING AND SAFETY
DOI	https://doi.org/10.31435/ijitss.2(50).2026.6141
RECEIVED	16 March 2026
ACCEPTED	22 June 2026
PUBLISHED	25 June 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

INTRADERMAL BOTULINUM TOXIN FOR ERYTHEMATOTELANGIECTATIC ROSACEA: MECHANISMS, DOSING AND SAFETY

Aleksandra Kujach *(Corresponding Author, Email: aleksandra.kujach@gumed.edu.pl)*
M.D., University Clinical Centre, Gdańsk, Poland
ORCID ID: 0009-0004-8338-136X

Julia Góralska
Medical University of Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0004-7594-0387

Melania Popielarczyk
Medical University of Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0000-0658-069X

Katarzyna Napiórkowska
M.D., Nicolaus Copernicus Hospital in Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0002-9736-9252

Dominik Płaza
Scientific Circle of Neurotraumatology, Department of Emergency Medicine, Medical University of Gdańsk, Gdańsk, Poland
ORCID ID: 0009-0000-6251-3969

ABSTRACT

Erythematotelangiectatic rosacea is a chronic inflammatory and neurovascular facial dermatosis characterized by persistent centrofacial erythema, flushing, telangiectasia, burning, stinging, and marked impairment of quality of life. Although topical alpha-adrenergic agonists, vascular lasers, intense pulsed light, systemic anti-inflammatory agents, and skin barrier-directed interventions are widely used, persistent erythema and flushing often remain difficult to control. Intradermal botulinum toxin type A has emerged as a promising off-label therapeutic option for refractory vascular rosacea. Its effect is no longer interpreted solely through neuromuscular blockade. Current evidence suggests that botulinum toxin type A may reduce erythema and flushing through modulation of acetylcholine-dependent vasodilation, inhibition of vasoactive neuropeptides such as substance P and calcitonin gene-related peptide, suppression of mast cell degranulation, interference with LL-37/MRGPRX2-mediated inflammation, downregulation of vascular endothelial growth factor-driven angiogenesis, and improvement of skin quality parameters including sebum production and pore appearance. Clinical studies, including case series, prospective cohorts, split-face trials, and meta-analyses, indicate reductions in erythema, flushing severity, vascular density, and patient-reported symptoms after intradermal or microdroplet injections. However, the literature remains limited by small sample sizes, heterogeneous dosing regimens, short follow-up, variable toxin formulations, and inconsistent outcome measures. This review summarizes the mechanistic rationale, clinical efficacy, injection protocols, safety profile, limitations, and future directions of intradermal botulinum toxin type A in erythematotelangiectatic rosacea.

KEYWORDS

Erythematotelangiectatic Rosacea; Botulinum Toxin Type A; Intradermal Injection; Microbotox; Microdroplet Technique; VEGF; Neurogenic Inflammation

CITATION

Aleksandra Kujach, Julia Góralska, Melania Popielarczyk, Katarzyna Napiórkowska, Dominik Płaza. (2026) Intradermal Botulinum Toxin for Erythematotelangiectatic Rosacea: Mechanisms, Dosing and Safety. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.6141

1. Introduction

Rosacea is a chronic inflammatory dermatosis characterized by recurrent centrofacial erythema, flushing, telangiectasia, papules, pustules, phymatous changes, ocular involvement, burning, stinging, and heightened skin sensitivity. Modern classification increasingly emphasizes a phenotype-based approach rather than rigid subtype categories, but erythematotelangiectatic rosacea (ETR) remains a clinically useful term for patients in whom persistent erythema, flushing, and telangiectasia predominate. ETR is particularly challenging because vascular symptoms often persist despite adequate control of inflammatory lesions. (Alsaati et al., 2023; Choe & Barbieri, 2023; Sharma et al., 2022)

Persistent facial erythema and flushing are not only visible signs of disease activity but also major determinants of psychosocial burden. Patients frequently report embarrassment, avoidance of social interactions, occupational limitations, reduced self-esteem, and anxiety related to facial redness. In this setting, treatment success cannot be measured only by lesion counts; patient-reported burning, flushing frequency, quality of life, and perceived disease control are also essential endpoints. (Takahashi et al., 2024)

Current treatment options for vascular rosacea include trigger avoidance, gentle skin care, photoprotection, topical brimonidine or oxymetazoline, vascular lasers, intense pulsed light, and systemic anti-inflammatory therapies when papulopustular lesions coexist. However, topical vasoconstrictors may provide transient benefit and may be limited by rebound erythema or incomplete response, whereas laser and light-based therapies require repeated sessions and may be poorly tolerated in highly sensitive skin. These limitations have encouraged investigation of intradermal botulinum toxin type A (BoNT-A) as an off-label approach for persistent erythema and flushing. (Yang et al., 2022)

BoNT-A has traditionally been used for neuromuscular indications and dynamic rhytides through inhibition of acetylcholine release at the neuromuscular junction. In rosacea, however, the therapeutic rationale is different. Intradermal or microdroplet injection aims to act within the skin rather than the muscle, targeting neurovascular signaling, inflammatory mediator release, mast cell activity, sebaceous gland function, and vascular reactivity while minimizing facial muscle weakness. (Dicker et al., 2025)

This review summarizes current evidence on intradermal BoNT-A in ETR, focusing on mechanisms, dosing, injection technique, clinical outcomes, safety, and practical limitations.

2. Methods

This article is a targeted narrative review based on the predefined corpus of publications selected for the manuscript topic. Priority was given to human studies evaluating intradermal, superficial, mesotherapy, microdroplet, or microbotox injection of BoNT-A for rosacea-associated erythema, flushing, skin quality, or vascular symptoms. Randomized controlled trials, split-face studies, prospective cohorts, case series, systematic reviews, meta-analyses, and mechanistic studies were considered.

Mechanistic studies were included when they addressed pathways relevant to rosacea, including mast cell activation, cathelicidin LL-37, MRGPRX2, vascular endothelial growth factor (VEGF), neurogenic inflammation, acetylcholine-mediated vasodilation, substance P, calcitonin gene-related peptide (CGRP), transient receptor potential vanilloid 1 (TRPV1), and angiogenesis. Publications concerning intradermal BoNT-A for skin quality, pores, sebum control, flushing syndromes, and vascular modulation were used where relevant to injection technique or mechanism. Articles unrelated to rosacea or intradermal BoNT-A were not used as primary evidence for efficacy.

Because the available literature is heterogeneous with respect to toxin formulation, dose, dilution, injection depth, injection spacing, comparator, rosacea phenotype, and outcome measures, no quantitative synthesis was performed in this review.

3. Pathophysiological Rationale for BoNT-A in ETR

3.1. Neurovascular dysregulation and cholinergic vasodilation

ETR is characterized by abnormal neurovascular regulation. Flushing episodes reflect transient vasodilation, whereas repeated episodes may contribute to persistent erythema and telangiectatic vascular remodeling. Acetylcholine released from autonomic cholinergic fibers can mediate cutaneous vasodilation, and BoNT-A may reduce flushing by inhibiting acetylcholine release within cutaneous autonomic pathways. This mechanism provides a plausible explanation for the reduction of flushing and erythema observed after intradermal BoNT-A injections. (Santillan et al., 2024)

The vascular effects of BoNT-A appear dose- and tissue-dependent. A recent narrative review proposed a dual model in which higher doses may enhance perfusion and angiogenesis through VEGF and nitric oxide pathways, whereas lower doses may reduce excessive cholinergic vasodilation and neurogenic inflammation, making low-dose intradermal BoNT-A particularly relevant for conditions such as rosacea and hyperhidrosis. (Nazari et al., 2026)

This distinction is clinically important. Rosacea protocols generally use diluted, intradermal, low-dose microdroplets intended to modulate superficial vascular reactivity, not high-dose muscular chemodenervation. Excessive dose, volume, or depth may increase the risk of unwanted facial weakness.

3.2. Neuropeptide inhibition: substance P, CGRP and VIP

Neurogenic inflammation contributes to flushing, burning, stinging, and vascular hyperreactivity in rosacea. Substance P, CGRP, vasoactive intestinal peptide, and other neuropeptides can promote vasodilation, mast cell activation, pain, pruritus, and inflammatory amplification. BoNT-A may inhibit the release of several of these mediators, providing a mechanistic bridge between toxin injection and reduction in flushing, burning, and stinging. (Hanna et al., 2022; Santillan et al., 2024)

This mechanism may be particularly relevant in patients who describe flushing as painful, burning, or trigger-sensitive rather than merely visible redness. It may also explain why patient-reported outcomes sometimes improve more clearly than objective erythema measurements.

3.3. Mast cells, LL-37 and MRGPRX2

Rosacea pathogenesis involves dysregulation of innate immunity, increased cathelicidin activity, and activation of mast cells. LL-37 can promote rosacea-like inflammation, and mast cells are key amplifiers of this pathway. Experimental work has shown that onabotulinumtoxinA and botulinum toxin B can inhibit compound 48/80-induced mast cell degranulation in both human and murine mast cells. In an LL-37-induced rosacea-like mouse model, onabotulinumtoxinA reduced erythema, mast cell degranulation, and mRNA expression of rosacea biomarkers. (Choi et al., 2019)

A more recent study further refined this mechanism by focusing on angiogenesis. In LL37-induced rosacea-like inflammation, BoNT/A reduced VEGF secretion by mast cells and inhibited endothelial proliferation and tube formation. The authors proposed that BoNT/A enhances LL37-mediated internalization of MRGPRX2 in mast cells, thereby reducing VEGF secretion, neovascularization, and facial flushing. (Wan et al., 2025)

This mast cell–MRGPRX2–VEGF axis is especially relevant to ETR because persistent erythema and telangiectasia are vascular phenotypes. Although the translational relevance of mouse and cell models requires further validation in human skin, these data support the concept that BoNT-A may act directly on inflammatory and vascular pathways rather than merely reducing muscle contraction.

3.4. TRPV1 and sensory hyperreactivity

TRPV1 is implicated in heat sensitivity, neurogenic inflammation, burning, pain, and vasodilation. Increased TRPV expression has been described in rosacea-affected skin, and BoNT-A has been proposed to reduce TRPV1 expression or downstream neurogenic signaling. In the 2025 split-face randomized study, the authors discussed TRPV1 modulation as one of several plausible mechanisms for erythema reduction after intradermal BoNT-A. (Dağtaş et al., 2025)

This mechanism remains inferential in clinical rosacea studies, but it is consistent with the clinical observation that BoNT-A may improve burning, stinging, and flushing sensitivity in selected patients.

3.5. Skin quality, sebum and pores

Although the primary therapeutic target in ETR is vascular erythema, intradermal BoNT-A may also improve skin quality. Microbotox protocols have been associated with reduced sebum, smaller pores, smoother texture, and improved skin appearance. The proposed mechanism involves inhibition of acetylcholine signaling in sebaceous glands, effects on sweat and sebaceous activity, and modulation of inflammatory signaling in dermal cells. (Calvisi et al., 2022; Santillan et al., 2024)

In rosacea, this effect should be interpreted as secondary rather than primary. Skin texture and pore improvement may enhance patient satisfaction, but the central disease-specific goal remains reduction of erythema, flushing, burning, and vascular hyperreactivity.

4. Injection Technique and Dosing

4.1. Intradermal versus intramuscular injection

The therapeutic concept in ETR is based on superficial intradermal or microdroplet delivery. The injection should produce small, visible blebs, indicating placement within the superficial dermis. If the solution flows too easily or no bleb is formed, the injection may be too deep, increasing the risk of diffusion into facial musculature. Proper depth is especially important in the cheeks, perioral region, chin, and lower face because inadvertent paralysis may produce asymmetry or oral incompetence. (Calvisi et al., 2022)

Anatomical caution is essential. A letter specifically warned that injection points near the depressor labii inferioris and depressor anguli oris can cause lower lip drooping, slurring, drooling, or perioral asymmetry if toxin diffuses into the wrong muscle. The authors also noted that overly lateral injection may reach the buccinator and cause buccal mucosal biting. (*Anatomical Exhortations of Botulinum Toxin Injections for Rosacea | Journal of Clinical and Aesthetic Dermatology | Professor Faisal Ali*, n.d.)

4.2. Microdroplet and microbotox concepts

Microbotox refers to multiple tiny aliquots of diluted BoNT-A injected intradermally or at the dermal–subdermal interface. In aesthetic contexts, it aims to reduce fine lines, pore size, oiliness, and skin laxity while avoiding deep muscle paralysis. In rosacea, the same technical principle is used to modulate superficial neurovascular and inflammatory pathways. (Fabi et al., 2023; Kandhari et al., 2022)

One review summarized a commonly used microbotox preparation: after standard dilution of 100 U onabotulinumtoxinA with 2.5 mL saline, 20, 24, or 28 U may be withdrawn into a 1-mL syringe and then diluted with 1% lidocaine to 1 mL; microdroplets are then injected into the skin at approximately 0.8-1 cm intervals. The same review emphasized that there is no standardized dosing regimen for flushing and that diluted intradermal injection is intended to widen coverage while reducing the risk of unintended muscle effects. (Santillan et al., 2024)

4.3. Published dosing regimens

Published protocols vary substantially. In the prospective microbotox study by Calvisi et al., a 50 U vial of onabotulinumtoxinA was reconstituted with 0.75 mL saline plus 0.5 mL lidocaine without adrenaline, yielding a total volume of 1.25 mL. Then, 0.5 mL containing 20 U was drawn and further diluted to 1 mL. Tiny droplets of approximately 0.01 mL, corresponding to approximately 0.2 U, were injected in a regular grid 1 cm^2 apart. Injections were performed with a 32-G needle, superficially enough to produce a small raised bleb. (Calvisi et al., 2022)

In the 2024 prospective open study by Takahashi et al., 100 U incobotulinumtoxinA was diluted in 4 mL saline, giving 0.25 U per 0.01 mL. Injections were performed at an intradermal depth of approximately 0.5 mm, with 0.5 cm spacing, using 31-32-G needles, and the maximum total dose was 70 U per participant, equivalent to up to 280 injection points. A second application was performed on day 14 if indicated in selected areas. (Takahashi et al., 2024)

In the 2025 split-face randomized controlled trial, 100 U onabotulinumtoxinA was diluted with 10 mL saline. One facial half received 15 U BoNT-A total, administered as 0.05 mL injections containing 0.5 U at each of 30 points spaced 0.5 cm apart. The contralateral control side received the same volume of saline injections. (Dağtaş et al., 2025)

In the 2022 Yang et al. study, 100 U BoNT-A was diluted in 6.25 mL saline, yielding 16 U/mL. Patients received 0.05 mL, corresponding to 0.8 U, at each injection point, with 1-cm spacing. The total dose ranged from 40 to 60 U per patient depending on the area of erythema and flushing. (Yang et al., 2022)

In the JAAD therapeutic pearl on mesotherapy, BoNT diluted to 10 U/mL was injected intradermally into the hypervascular and telangiectatic centrofacial area as 0.05-mL microdroplets spaced 0.5 cm apart. The authors reported visible improvement within 1-2 weeks and suggested repeat treatment every 4-5 months to maintain remission. (Bharti et al., 2023; Yeh et al., 2025)

4.4. Practical dosing implications

The available evidence suggests several practical principles. First, lower volumes per injection point may reduce the risk of muscular diffusion. A 2025 scoping review and meta-analysis reported that unwanted facial muscle paralysis was seen across several toxin concentrations but was not reported in studies using less than 0.02 mL per injection site. (Yeh et al., 2025)

Second, total dose should be individualized according to the involved area, skin thickness, prior toxin exposure, facial anatomy, and risk tolerance. Third, perioral and lower-face injections should be approached more conservatively than cheek injections. Fourth, repeated treatment is often necessary because clinical effects commonly decline after several months.

5. Clinical Evidence

5.1. Early case reports and case series

The earliest evidence consisted largely of case reports and small series. Dayan et al. reported improvement in rosacea-related erythema and flushing with onabotulinumtoxinA microdroplets, using approximately 8-12 U per affected cheek with 0.5-cm spacing, with repeated treatment in some cases. (Alsaati et al., 2023)

Bloom et al. evaluated intradermal abobotulinumtoxinA in patients with ETR and reported significant reduction in erythema at one month, persisting up to three months. The study was limited by lack of a control group and small sample size, but it helped establish the feasibility of intradermal BoNT-A for facial erythema. (Hanna et al., 2022)

Park et al. treated patients with recalcitrant and persistent ETR using intradermal BoNT-A and reported significant improvement in erythema from week 1 to week 8, with improved patient satisfaction. However, transient abnormal facial expressions led to discontinuation in several participants, underscoring the importance of dose and injection depth. (Hanna et al., 2022)

5.2. Prospective microbotox study

Calvisi et al. prospectively evaluated microbotox in 50 patients, including 15 with ETR and 35 with mild-to-moderate acne. The ETR group received two intradermal BoNT-A treatments at 14-day intervals. By one week after the second session, patients showed aesthetic improvement; after two weeks, erythema and flushing decreased, skin quality improved, and DLQI improved. The authors reported no major adverse events, no rebound flaring, and stable results at four months. (Calvisi et al., 2022)

The same study reported a mean DLQI improvement greater than 54.66% and a Subject Global Aesthetic Improvement Scale value of 3.46 in the rosacea subgroup, although the open-label uncontrolled design limits causal interpretation. (Calvisi et al., 2022)

5.3. Prospective open study with quality-of-life endpoints

Takahashi et al. conducted a prospective, interventional, open, uncontrolled study in 33 individuals with rosacea who received standard treatment according to subtype plus superficial BoNT injections, with follow-up for 90 days. BoNT injections were applied on days 1 and 14. Improvement in clinical signs was reported by investigators and by 94% of participants. Quality of life improved significantly, and Rosenberg self-esteem scores increased markedly. (Takahashi et al., 2024)

In the same study, WHOQoL-Bref scores increased from 91.39 to 95.29, RosaQoL scores decreased from 72.42 to 65.16, indicating improved rosacea-specific quality of life, and Rosenberg self-esteem scores increased from 28.19 to 32.65 after three months, (Takahashi et al., 2024)

These data are important because they capture patient-centered outcomes, but the lack of a control group and concomitant standard treatments make it difficult to isolate the independent effect of BoNT-A.

5.4. Longitudinal efficacy over six months

Yang et al. enrolled 16 female patients with refractory ETR. Injections were delivered at 1-cm intervals, with 0.8 U per point and a total dose of 40–60 U per patient. CEA scores improved from 2.88 ± 0.62 at baseline to 1.00 ± 0.37 at one month. Flushing scores decreased from 47.81 ± 8.68 at baseline to 18.75 ± 3.86 at one month, 20.19 ± 4.26 at three months, and 26.50 ± 7.93 at six months. DLQI similarly improved at one and three months but worsened somewhat by six months, suggesting gradual decline of effect. (Yang et al., 2022)

Adverse events in this study were mild and self-limited. Injection pain was universal but tolerable; four patients had transient increased erythema after injection, five had bruising, three reported tightness, and one developed mild asymmetry while smiling, which resolved within one month. No serious allergic reactions, respiratory symptoms, generalized weakness, or fatigue were reported. (Yang et al., 2022)

This study is valuable because it provides longer follow-up than many earlier reports and suggests that retreatment may be considered around five to six months in selected patients.

5.5. Randomized split-face evidence and objective measurements

The 2025 prospective randomized controlled double-blind split-face study represents one of the strongest clinical designs available. Thirty patients aged 18–60 years with ETR received 15 U BoNT-A on one facial half and saline on the contralateral half. Objective outcomes included Mexameter erythema index, clinician erythema assessment, dermatoscopic background erythema, and videocapillaroscopic vascular structure and density. (Dağtaş et al., 2025)

At one month, the BoNT-A side showed significant reductions in erythema index from 517.0 ± 97.4 to 413.9 ± 115.5, whereas the saline side showed no significant change. CEA scores decreased from 1.9 ± 0.9 to 1.4 ± 0.7 on the BoNT-A side, while remaining unchanged on the saline side. Dermoscopic erythema decreased in 63.3% of BoNT-A-treated halves compared with 23.3% of saline-treated halves, and IGA scores based on capillaroscopic vascular assessment showed significantly better response on the BoNT-A side. (Dağtaş et al., 2025)

Patient self-assessment scores improved on both sides, likely reflecting the difficulty patients had distinguishing treated from control halves in a double-blind split-face design. The objective asymmetry between sides supports a true treatment effect despite bilateral subjective improvement. (Dağtaş et al., 2025)

5.6. Evidence from systematic reviews and meta-analyses

A 2023 systematic review included 17 studies and concluded that intradermal BoNT-A significantly alleviated facial erythema and flushing and improved quality of life or patient satisfaction. The same review reported recurrence at three to six months in some patients and pooled post-injection adverse-event rates of localized erythema, ecchymosis, and facial muscle affection of 24.6%, 5.1%, and 4.3%, respectively. (Alsaati et al., 2023)

A 2024 systematic review and meta-analysis on cutaneous flushing included nine studies and 132 patients, including rosacea and non-rosacea flushing etiologies. Clinical flushing scores decreased by 1.25 points at one month after BoNT treatment. DLQI decreased by approximately 9 points, although the quality-of-life estimate did not reach statistical significance. The authors emphasized heterogeneity in patient factors, flushing etiology, dosing, outcome scales, and limited sample size (Vincent et al., 2024)

A 2025 scoping review and meta-analysis focusing specifically on intradermal BoNT-A for rosacea erythema included seven studies with 167 patients. Meta-analysis of two randomized controlled trials showed significant erythema improvement at month three, and single-arm analyses showed significant improvement at one, two, and three months. However, the authors highlighted heterogeneity and small sample size, and they emphasized that facial muscle complications were not observed when the volume per site was below 0.02 mL. (Yeh et al., 2025)

A more recent systematic review limited to randomized trials in ETR identified three RCTs involving 62 adult participants and concluded that BoNT-A reduced facial erythema and flushing with mild, transient, self-limited adverse events. The authors nevertheless stressed that evidence remains limited by small sample sizes, heterogeneous protocols, and short follow-up. (Marrar et al., 2026)

6. Combination Therapy

6.1. BoNT-A with vascular devices

Vascular lasers and intense pulsed light target telangiectasia and persistent erythema through photothermolysis, while BoNT-A may reduce neurovascular hyperreactivity and flushing. This creates a plausible rationale for combination therapy, particularly in patients with both fixed vascular change and episodic flushing.

A randomized split-face study of 22 patients evaluated BoNT-A plus broadband light (BBL) versus BBL plus saline. The experimental side showed greater improvement in global flushing symptom score, VISIA red value, erythema index, transepidermal water loss, sebum secretion, and hydration compared with BBL alone. One patient had transient limitation of mouth-corner elevation, which resolved after one month. (Tong et al., 2022)

A review also described pulsed dye laser followed by intradermal BoNT-A, with lasting improvement of erythema and flushing after three treatment sessions and follow-up to nine months. (Santillan et al., 2024)

These findings suggest that BoNT-A may be useful as a vascular stabilizer before or after device-based therapy. However, the optimal sequence, interval, and patient phenotype remain undefined.

6.2. BoNT-A with oral doxycycline

In a randomized controlled trial of 46 participants with moderate-to-severe rosacea, intradermal BoNT-A plus oral doxycycline was compared with doxycycline plus normal saline. Both groups received doxycycline, while the combination group received BoNT-A diluted to 10 U/mL, injected intradermally at 1-cm intervals with 0.025 mL per site. The mean BoNT-A dose was 30.70 ± 1.93 U per patient. Combination therapy produced greater reductions in CEA, GFSS, IGA, and DLQI than doxycycline plus saline, while adverse events such as injection-site pain, erythema, and edema were tolerable and comparable between groups. (Nguyen et al., 2026)

This trial is clinically relevant because many rosacea patients present with mixed vascular and inflammatory features. Doxycycline may reduce inflammatory pathways, whereas BoNT-A may target flushing and neurovascular hyperreactivity. Nevertheless, additional trials are needed to determine whether BoNT-A should be used only in refractory cases or earlier in moderate-to-severe disease.

6.3. BoNT-A with aesthetic combination regimens

The broader aesthetic literature increasingly examines combinations of BoNT-A with biostimulators, dermal fillers, hyaluronic acid, microneedling, lasers, radiofrequency, and focused ultrasound. A systematic review of biostimulator combinations found potential aesthetic benefits but emphasized heterogeneous protocols, small studies, inconsistent outcomes, and limited mechanistic understanding. (Tam et al., 2025)

For ETR, such literature should be applied cautiously. Rosacea skin is sensitive and barrier-impaired, and aggressive combination regimens may provoke irritation. BoNT-A may be combined rationally with vascular devices or anti-inflammatory therapy, but combination with fillers, biostimulators, or energy-based rejuvenation procedures should not be presented as disease-specific rosacea therapy unless supported by rosacea-specific data.

7. Safety and Tolerability

Overall, intradermal BoNT-A appears well tolerated in ETR, but adverse events are not negligible. Common local events include injection pain, bruising, transient erythema, edema, tenderness, and localized discomfort. These are usually mild and self-limited.

In Yang et al., all 16 patients reported slight injection pain, four had transient increased erythema, five had bruising, three had temporary tightness, and one had mild smile asymmetry; all resolved without serious sequelae. (Yang et al., 2022)

In the 2025 randomized split-face study, mild tenderness and bruising were the most common local events. One patient developed transient facial muscle paresis on the BoNT-A-treated side on day 10; it resolved completely by day 40 without intervention. The authors reported no adverse events requiring hospitalization. (Dağtaş et al., 2025)

In Calvisi et al., ETR patients reported mild pain during treatment and occasional localized bruising that resolved spontaneously; no major side effects, rebound flaring, or mimic impairment were reported. (Calvisi et al., 2022)

The most clinically important preventable complication is unwanted facial muscle weakness. This risk increases when injection volume is high, injections are too deep, or toxin is placed near muscles controlling oral competence, smiling, blinking, or lower-lip position. The lower face, chin, perioral region, and lateral cheek require particular anatomical caution. (*Anatomical Exhortations of Botulinum Toxin Injections for Rosacea | Journal of Clinical and Aesthetic Dermatology | Professor Faisal Ali*, n.d.)

Rare hypersensitivity reactions to cosmetic BoNT-A have been reported in the broader literature, including mild allergic reactions, delayed hypersensitivity, and serum sickness-like reactions. These appear uncommon but should be considered in patients with prior toxin reactions, multiple exposures, or unexplained systemic symptoms after injection. (Buchholz et al., 2025; DeLuca-Pytell et al., 2026; Li et al., 2024)

8. Practical Clinical Positioning

At present, intradermal BoNT-A should be considered an off-label adjunctive option for selected patients with ETR or vascular-predominant rosacea, especially when persistent erythema and flushing remain inadequately controlled by conventional therapy. The most appropriate candidates may include patients with refractory flushing, trigger-induced erythema, burning or stinging associated with vascular reactivity, and intolerance or incomplete response to topical vasoconstrictors or vascular devices.

BoNT-A is not a replacement for foundational rosacea care. Gentle cleansing, moisturization, photoprotection, trigger avoidance, treatment of inflammatory lesions, and management of barrier dysfunction remain necessary. BoNT-A is best conceptualized as a neurovascular modulator rather than an etiologic cure.

A conservative practical approach would include: careful diagnosis of ETR phenotype; avoidance of active dermatitis, infection, pregnancy, neuromuscular disease, or recent toxin exposure; use of diluted toxin; intradermal bleb technique; small injection volumes; avoidance of high-risk perioral zones; photographic and objective erythema assessment; and follow-up at one to three months. Retreatment may be considered around three to six months depending on recurrence and patient preference.

9. Future Directions

Future trials should be larger, randomized, double-blind, and adequately powered. They should stratify patients by rosacea phenotype, baseline flushing frequency, persistent erythema severity, telangiectasia burden, skin sensitivity, prior laser exposure, topical vasoconstrictor response, and inflammatory lesion count.

Standardized protocols are needed. Trials should compare different concentrations, volumes, injection depths, and spacing intervals while maintaining product-specific unit clarity. The relationship between dose per point, volume per point, total dose, efficacy duration, and facial muscle adverse events should be specifically studied.

Objective outcome measures should include clinician erythema scales, validated flushing scales, Mexameter erythema index, standardized photography, dermoscopy, videocapillaroscopy, VISIA or comparable imaging, patient-reported burning/stinging scores, DLQI, RosaQoL, and relapse timing. Mechanistic substudies could include skin biopsies, mast cell markers, VEGF, LL-37, MRGPRX2, TRPV1, CGRP, substance P, and vascular density.

Finally, future studies should clarify where BoNT-A fits in the therapeutic sequence: as rescue therapy for refractory ETR, as adjunct to vascular lasers, as a periodic maintenance treatment, or as part of combined therapy for moderate-to-severe rosacea with both vascular and inflammatory components.

10. Conclusions

Intradermal BoNT-A is a promising off-label therapy for ETR, particularly in patients with persistent erythema and flushing refractory to conventional management. Its therapeutic effect is likely multifactorial, involving inhibition of acetylcholine-mediated vasodilation, suppression of neuropeptides, modulation of mast cell degranulation, reduction of LL-37/MRGPRX2-driven inflammation, inhibition of VEGF-related angiogenesis, and improvement of skin quality parameters.

Clinical evidence supports reductions in erythema, flushing, vascular density, and patient-reported symptoms, with effects typically emerging within one to two weeks and lasting approximately three to six months. The strongest data come from split-face randomized studies and recent meta-analyses, but the literature remains limited by small samples, short follow-up, and heterogeneous protocols.

Safety is generally favorable when BoNT-A is injected superficially, in small volumes, and with careful anatomical planning. The main preventable adverse event is unwanted facial muscle weakness due to excessive dose, large injection volume, or deep placement. For now, intradermal BoNT-A should be considered a valuable adjunctive option rather than a standardized first-line therapy. High-quality trials are needed to define optimal dosing, treatment intervals, patient selection, and long-term safety.

REFERENCES

1. Alsaati, A. A., Alsaadoun, D., Kinkar, L. I., Alkhamis, R. S., Ahmed, W. A., & Almathami, A. H. (2023). The efficacy and safety of botulinum toxin A for the treatment of rosacea: A systematic review. Cureus, 15(12). https://doi.org/10.7759/cureus.51304
2. Anatomical exhortations of botulinum toxin injections for rosacea | Journal of Clinical and Aesthetic Dermatology | Professor Faisal Ali. (n.d.). Retrieved June 14, 2026, from https://www.dralidermatology.com/publications/anatomical-exhortations-of-botulinum-toxin-injections-for-rosacea-journal-of-clinical-and-aesthetic-dermatology/
3. Bharti, J., Sonthalia, S., & Jakhar, D. (2023). Mesotherapy with botulinum toxin for the treatment of refractory vascular and papulopustular rosacea. Journal of the American Academy of Dermatology, 88(6), e295–e296. https://doi.org/10.1016/j.jaad.2018.05.014
4. Buchholz, E., Wanitphakdeedecha, R., Jaturawichanant, S., Pattanapran, K., & Corduff, N. (2025). Hypersensitivity reactions associated with aesthetic botulinum toxin A injections: A case series. Cureus, 17(10), e95795. https://doi.org/10.7759/cureus.95795
5. Calvisi, L., Diaspro, A., & Sito, G. (2022). Microbotox: A prospective evaluation of dermatological improvement in patients with mild-to-moderate acne and erythematotelangiectatic rosacea. Journal of Cosmetic Dermatology, 21(9), 3747–3753. https://doi.org/10.1111/jocd.14692
6. Choe, J., & Barbieri, J. S. (2023). Emerging medical therapies in rosacea: A narrative review. Dermatology and Therapy, 13(12), 2933–2949. https://doi.org/10.1007/s13555-023-01048-1
7. Choi, J. E., Werbel, T., Wang, Z., Wu, C. C., Yaksh, T. L., & Di Nardo, A. (2019). Botulinum toxin blocks mast cells and prevents rosacea-like inflammation. Journal of Dermatological Science, 93(1), 58–64. https://doi.org/10.1016/j.jdermsci.2018.12.004
8. Dağtaş, B. B., Erdem, O., Gneç, T. İ., Avci, E. B., Manav, V., & Koku Aksu, A. E. (2025). Effects of botulinum toxin type A treatment on clinical and biophysical parameters in patients with erythematotelangiectatic rosacea: A prospective, randomized, controlled, double-blind study. Dermatologic Surgery: Official Publication for American Society for Dermatologic Surgery, 51(5), 515–521. https://doi.org/10.1097/dss.0000000000004528
9. DeLuca-Pytell, D., Dass, K., Audia, G., & Busuito, E. (2026). Serum sickness after cosmetic botulinum toxin type A injections. Aesthetic Surgery Journal Open Forum, 8. https://doi.org/10.1093/asjof/ojag027
10. Dicker, V., Serna Posada, M. del M., Galeano Piedrahita, E., Vasquez Villegas, S., & Perez Madrid, C. (2025). Intradermal microdroplet injection of standard-diluted incobotulinumtoxin A for the treatment of erythematotelangiectatic rosacea: A study from a dermatology center in Medellín, Colombia. Cureus. https://doi.org/10.7759/cureus.78957
11. Fabi, S. G., Park, J. Y., Goldie, K., & Wu, W. (2023). Microtoxin for improving pore size, skin laxity, sebum control, and scars: A roundtable on integrating intradermal botulinum toxin type A microdoses into clinical practice. Aesthetic Surgery Journal, 43(9), 1015–1024. https://doi.org/10.1093/asj/sjad044
12. Hanna, E., Xing, L., Taylor, J. H., & Bertucci, V. (2022). Role of botulinum toxin A in improving facial erythema and skin quality. Archives of Dermatological Research, 314(8), 729–738. https://doi.org/10.1007/s00403-021-02277-0
13. Kandhari, R., Kaur, I., Gupta, J., & Al-Niaimi, F. (2022). Microdroplet botulinum toxin: A review. Journal of Cutaneous and Aesthetic Surgery, 15(2), 101–107. https://doi.org/10.4103/jcas.jcas_162_21
14. Li, Y., Zheng, Q., Lin, J., Su, X., Zhuang, J., Wei, Q., & Hu, J. (2024). Mild allergic reactions after botulinum toxin injection: A case series and literature review. Plastic and Reconstructive Surgery Global Open, 12(5), e5845. https://doi.org/10.1097/gox.0000000000005845
15. Marrar, K., Althiyabi, R., Alsannaa, M., Alfalah, R., Soroje, J., Anbar, E., Al Ibrahim, I., & Al Awadhi, A. (2026). Therapeutic efficacy and safety of botulinum toxin type A in erythematotelangiectatic rosacea: A systematic review. Cureus, 18(4). https://doi.org/10.7759/cureus.106841
16. Nazari, S., Sadeghi, M. S., Pourani, M. R., Muñoz-Gonzalez, C., & Fakih-Gomez, N. (2026). Botulinum toxin vascular effectiveness: Low or high doses? Aesthetic Plastic Surgery. https://doi.org/10.1007/s00266-026-05685-7
17. Nguyen, T. T., Le, D. H., Vu, H. T., Vu, L. H., Vu, M. N., & Pham, P. T. M. (2026). Combination therapy with oral doxycycline and intradermal botulinum toxin type A for moderate-to-severe rosacea: A randomized controlled trial. Indian Journal of Dermatology, 71(2). https://doi.org/10.4103/ijd.ijd_654_24
18. Santillan, M. R., Ozog, D., & Wu, W. (2024). Using neuromodulators to improve scar formation, keloids, rosacea, and antiaging. Dermatologic Surgery: Official Publication for American Society for Dermatologic Surgery, 50(9S), S91–S96. https://doi.org/10.1097/dss.0000000000004353
19. Sharma, A., Kroumpouzos, G., Kassir, M., Galadari, H., Goren, A., Grabbe, S., & Goldust, M. (2022). Rosacea management: A comprehensive review. Journal of Cosmetic Dermatology, 21(5), 1895–1904. https://doi.org/10.1111/jocd.14816

20. Takahashi, K. H., Utiyama, T. O., Bagatin, E., Picosse, F. R., & Almeida, F. A. (2024). Efficacy and safety of botulinum toxin for rosacea with positive impact on quality of life and self-esteem. International Journal of Dermatology, 63(5), 590–596. https://doi.org/10.1111/ijd.17040
21. Tam, E., Choo, J. P. S., Rao, P., Webb, W. R., Carruthers, J. D. A., & Rahman, E. (2025). A systematic review on the effectiveness and safety of combining biostimulators with botulinum toxin, dermal fillers, and energy-based devices. Aesthetic Plastic Surgery, 49(10), 2809–2833. https://doi.org/10.1007/s00266-024-04627-5
22. Tong, Y., Luo, W., Gao, Y., Liu, L., Tang, Q., & Wa, Q. (2022). A randomized, controlled, split-face study of botulinum toxin and broadband light for the treatment of erythematotelangiectatic rosacea. Dermatologic Therapy, 35(5). https://doi.org/10.1111/dth.15395
23. Vincent, N., Ravipati, A., Reynolds, J. M., & Kaufman, J. (2024). Efficacy of botulinum toxin in the treatment of cutaneous flushing: A systematic review and meta-analysis. Dermatologic Surgery: Official Publication for American Society for Dermatologic Surgery, 50(4), 354–359. https://doi.org/10.1097/dss.0000000000004073
24. Wan, J., Le, Y., Geng, M. M., Dong, B. Q., Liao, Z. K., Liu, L. X., & Lei, T. C. (2025). The anti-angiogenic effect of microbotox on rosacea is due to the suppressed secretion of VEGF by mast cells resulting from internalization of the MRGPRX2 receptor. Annals of Dermatology, 37(4), 228–240. https://doi.org/10.5021/ad.24.171
25. Yang, R., Liu, C., Liu, W., Luo, J., Cheng, S., & Mu, X. (2022). Botulinum toxin A alleviates persistent erythema and flushing in patients with erythema telangiectasia rosacea. Dermatology and Therapy, 12(10), 2285–2294. https://doi.org/10.1007/s13555-022-00784-0
26. Yeh, M. C. H., Shih, Y. C., & Huang, Y. C. (2025). Intradermal injection of botulinum toxin for erythema in rosacea: A scoping review and meta-analysis. Indian Journal of Dermatology, Venereology and Leprology, 91(4), 448–454. https://doi.org/10.25259/ijdvl_274_2024