Botulinum Toxin Off-Label Use in Dermatology: A Review

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Keywords

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Abstract

Background: Botulinum toxin is a neurotoxin produced by the bacterium *Clostridium botulinum* which causes a flaccid muscle paralysis. It is currently used for aesthetic treatments and in the focal hyperhidrosis. Recently, botulinum toxin has also been used experimentally in many other dermatological conditions with good results. **Objective:** To review and analyze the possible botulinum toxin off-label applications published. **Methods:** A retrospective review of the published data was conducted. **Conclusions:** this potent drug can lead to several off-label indications of interest for dermatologists. Further clinical trials are still needed to better understand the real efficacy and safety of these applications and to standardize injection and dose protocols.

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Introduction

Botulinum toxin type A (BoNT-A) blocks the release of acetylcholine and many other neurotransmitters from presynaptic vesicles by deactivating SNARE proteins. BoNT-A has a long history of therapeutic application in

focal hyperhidrosis, aesthetic medicine and neurological conditions with a strong efficacy and safety profile [1–7]. The enormous therapeutic potential of this drug contributed to a number of broad applications, especially in dermatological diseases. A large number of these indications are still lacking shared, approved protocols for dilution, doses, and timing of follow-up and retreatment. Also the injection techniques are still debated, depending on the operator's experience, angle of injection and depth. We have previously published a novel injection approach consisting in a needle adaptor that ensures a uniform administration of the toxin [3]. The aim of this review was to collect and analyze the published data concerning the most relevant off-label indications of BoNT-A.

Methods

A PubMed search from 1950 to July 2016 was performed to identify any reports on the use of botulinum toxin in off-label indications concerning dermatology. We detected these articles using the terms “botulinum toxin dermatology,” “botulinum toxin treatment,” “botulinum toxin off-label,” and meshed with a secondary search of studies pertaining to each indication. Only studies in English were reviewed. All studies that met the criteria were included and summarized in this review.

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Keloids and Hypertrophic Scars

Keloids and hypertrophic scars represent an aberrant response to the wound healing process. These scars are characterized by dysregulated growth with excessive collagen formation, and can be cosmetically and functionally troublesome to patients [8]. As recently reviewed, we currently have a lot of therapeutic tools to manage hypertrophic and keloid scars, but none of them is definitive; we are already unable to prevent an aberrant wound healing in predisposed patients [9]. Massage therapy [10], silicone dressings [11], gel containing onion extract [12], intralesional (IL) corticosteroid [13], laser therapy [14], surgical excision, radiotherapy [15], cryotherapy [16], and immune-response modulator [17] are only some of the numerous treatments proposed until now. A major factor determining the final cosmetic appearance of a cutaneous scar is the tension acting on the wound edges during the healing phase [17]. In 2000, Gassner et al. [18] hypothesized that the injections of BoNT-A can paralyze the musculature subjacent to a cutaneous defect and minimize the repetitive tensile forces on the wound edges, resulting in superior cosmetic outcome in the final scar. The study was conducted on a primate model and concerned only facial wounds after symmetrical surgical excision on the forehead (6 scars per animal, a total of 36 scars). A total dose of 21 U of BTX-A per half forehead was injected; the control side was injected with an equal volume of 0.9% saline alone. Subsequently, all of the wounds were closed with the same sutures. Three blinded observers evaluated the cosmetic appearance of the scars at 1, 4, and 12 weeks postoperatively. Twelve weeks postoperatively, a biopsy punch of the scars was obtained using a 4-mm punch. The observers, using a consensus score of evaluation, assessed the experimental sides as better than the control sides in all 6 animals. A new technique that effectively minimizes tension on the healing wound edges consists in inducing temporary paralysis of the muscle underlying a wound during revision surgery. Wilson [19] enrolled 55 patients in order to demonstrate the efficacy of botulinum toxin injections as a preventive agent in unfavorable wounds of the face after surgical revision. The results demonstrated that temporary paralysis of the muscle underlying a wound during revision surgery is an effective technique not only in primates, but also in humans, with a high satisfaction rate. In 2009, Xiao's group published 2 trials that investigated the therapeutic role of BoNT-A on hypertrophic scars. In this prospective clinical study, the authors enrolled 19 patients with 1-year follow-up [20]. At 1-month intervals,

botulinum toxin BoNT-A (2.5 U per cubic centimeter of lesion, not exceeding 100 U per patient in 1 injection) was injected in these patients for a total of 3 months. The promising results supported a new trial that included 12 patients with one or more keloids; the injection regimen was 70–140 U per session, at 3-month intervals for a maximum of 9 months [21]. Improvement was evaluated in both studies with patient and observer assessment using a 5-point scale and with photographic support in order to estimate the flattening and reduction of the scars. The study by Gauglitz's group [22] in 2012 introduced an objective evaluation of BoNT-A-treated keloids using optical 3-D profilometry; this technique did not reveal any changes after BoNT-A therapy compared with baseline in only 4 patients. Also, no *in vitro* effects of BoNT-A on TGF- β subtypes or fibroblast proliferation could be found. The first randomized, double-blind, comparison study of BoNT-A versus IL corticosteroid therapy in 24 patients with keloids has been recently published [22]. IL corticosteroid therapy with triamcinolone acetonide is regarded by many to be the first line of therapy in the treatment of keloids [13]. The patients were randomly divided into 2 equal groups: receiving IL steroid repeated every 4 weeks for 6 sessions (group A) and IL BoNT-A 5 IU/cm³ repeated every 8 weeks for 3 sessions (group B). Objective parameters (hardness, elevation, and redness), subjective symptoms (itching, pain, and tenderness), patient satisfaction, and side effects were evaluated. All the lesions were significantly decreasing in volume after treatment in both groups. A significant softening of lesions versus baseline was observed, with statistically significant improvement, in group A. There was a significant decrease in the size of lesions and in redness score compared with baseline, with no significant difference between both groups. Patients in group B reported a more significant reduction of their subjective complaints. Skin atrophy and telangiectasia were evident in 3 patients of group A (25%). The authors explained that these results were due to the ability of the BoNT-A to better control the small-fiber neuropathy causing itching, pain, and allodynia in patients affected by keloids [23]. More recently, using a rabbit ear hypertrophic scar model, BoNT-A revealed less improvement in hypertrophic index, fibroblast density, and relative collagen density compared with IL triamcinolone acetonide and 5-fluorouracil [21]. Table 1 presents only the studies conducted on human subjects. The main limitations in the use of BoNT-A for hypertrophic and keloid scars concern the high cost of this drug and the potential effect on normal skin surrounding the wound. However, the available studies reveal a great

Table 1. Studies on the application of botulinum toxin type A (BoNT-A) injections in keloids and hypertrophic scars

First author [Ref.], year	Type of study	n	BoNT-A doses	Outcomes	Follow-up	Results
Elhefnawy [21], 2016	Prospective	20	Once a month for 3 months, injected until slight blanching occurred	Therapeutic satisfaction of the patient and physician. Lesions were assessed for erythema, itching, and pliability; each item was assessed on a 5-point scale	6 months	Therapeutic satisfaction was “good” in 14 patients, “excellent” in 6; the mean erythema score decreased from 3.2 to 1.0, the mean pliability score from 3.3 to 0.8 and the mean itching score from 2.7 to 0.7; all of these were statistically significant
Shaarawy [19], 2015	Randomized, versus IL corticosteroid	24	5 IU/cm ³ repeated every 8 weeks for three sessions	Objective parameters (hardness, elevation, and redness), subjective complaints (itching, pain, and tenderness), patient satisfaction	6 months	Subjective symptoms improved more significantly in the BoNT-A group
Lee [22], 2015	Case report, BoNT-A associated with 595-nm pulsed dye laser	2	6–8 U	Not reported	Not reported	Improvement
Gauglitz [18], 2012	Prospective, uncontrolled	4	70–140 Speywood units per session injected every 2 months for up to 6 months	Differences in height and volume were evaluated clinically and measured with a 3-D optical profiling system; real time-PCR, MTT, and BrdU assays to analyze the effects on fibroblast proliferation and metabolism	Not reported	No regression of keloid tissue; no differences in expression of markers and cell proliferation; metabolism of keloid fibroblasts was not affected by BoNT-A treatment
Xiao [16], 2009	Prospective, randomized, uncontrolled	19	2.5 U per cm ³ of lesion once a month for a total of 3 months	Observer and patient satisfaction; photographic records; erythema, pliability and itching sensation were evaluated with a 5-point scale	6 months	Erythema, itching sensation, and pliability scores after the BTX-A injection all were significantly lower than before the BoNT-A injection; rate of therapeutic satisfaction was high
Xiao [17], 2009	Prospective, uncontrolled	12	70–140 U per session, every 3 months for maximum 9 months	Decrease in size and flattening of the lesion with 5-point scale; patient satisfaction	1 year	Regression from the periphery and a significant decrease in size was noted in all of the patients besides flattening of the lesions; very high patient satisfaction
Wilson [15], 2006	Prospective, uncontrolled	55, 40 completed follow-up	1.5 U per cm of wound length, in a linear pattern after surgical revision of facial scars	Patient satisfaction, photographic assessment	15.3 months mean	Thirty patients rated the improvement as marked (75%)
IL, intralesional.						

potential of this neurotoxin that deserves a more structured and numerous trials [23–26]. In fact, the literature is currently lacking randomized, double-blind, controlled trials on a consistent group of human beings, designed to investigate the efficacy in prevention and therapy of hypertrophic scars located not only in the facial district, but

also in body parts such chest or back, where muscles are large and strong. Subsequently, it would be desirable to establish an injection regimen and technique specific for this challenging indication. Table 1 resumes all the studies concerning the BoNT-A application in keloids and hypertrophic scars.

Hailey-Hailey Disease

Hailey-Hailey disease (HHD) or familial benign pemphigus is a chronic autosomal dominant acantholytic dermatosis, characterized by flaccid blistering lesions and erosions involving predominantly intertriginous parts of the body. This condition is exacerbated by heat, sweat, and bacterial colonization [27]. All these local factors can intensify the loss of cohesion among the keratinocytes and therefore the appearance of lesions on the intertriginous regions, mainly axillary and inguinal folds [28]. Treatment is intended to reach a remission, partial or complete, as long as possible. Topical, IL, and oral steroids, cyclosporine, methotrexate, antimicrobial agents, retinoids, tacrolimus, phototherapy, and other anecdotal treatments have been described. Surgical approaches include carbon dioxide laser ablation, cryotherapy, dermabrasion, electrosurgery, excision, and grafting [29]. Lapiere et al. [30] in 2000 introduced the first, successful, application of botulinum toxin (BoNT-A) in a patient affected by HHD after a number of conventional treatment failures. They treated only the axillary folds, first only the left axilla with 25 U, and after 6 months with 50 U for each axilla; they did not observe worsening or improvement of the groin. The authors suggested that the success of the BoNT-A injections was linked to the reduction of sweat production and consequently of the moisture that triggers microbial growth. Konrad and Petersen [31] compared BoNT-A treatment with ablative therapy (erbium:YAG laser). They injected BoNT-A on both sides of the submammary region, and after 4 days they used dermabrasion or erbium:YAG laser in a limited area of 25 cm² on each side. BoNT-A and ablative treatments were both capable of inducing remissions of HHD. In 2002, Kang and Yoon [32] confirmed the usefulness of BoNT-A in a recalcitrant HHD case; they treated both the inguinal and axillary folds with a 6-month remission. In 2008, Koeyers et al. [33] described 6 patients with extensive HHD resistant to multiple therapeutic regimens. They observed a marked improvement in all cases after BoNT-A treatment and defined BoNT-A as an effective and safe adjuvant treatment for extensive HHD. Bessa et al. [28] confirmed the efficacy of BoNT-A therapy in 2 sisters affected by HHD. Three patients were treated by Lopez-Ferrer and Alomar [34] with various regimens and timing of administration. In 2015, Bedi and Taylor [35] described a severe HHD case that involved perianal, perivulvar, and vaginal area, which was treated with cyclosporine, methotrexate and then with oral tacrolimus. This last regimen

led to a marked improvement, and BoNT-A therapy was administrated as an adjuvant therapy for lesions that still affected the intergluteal cleft. Ho and Jagdeo [36] obtained excellent improvement using onabotulinum toxin A with a 3-month remission. These reports show the efficacy of BoNT-A therapy in HHD, but the injection regimen and timing of re-administration are various and not well-established. Recently, Bagherani and Smoller [27] suggested more robust studies in order to confirm the role of BoNT-A in HHD therapy; maybe these further studies will conduct to a common injection protocol. Table 2 collects all the studies on the use of BoNT-A therapy in HHD.

Linear IgA Bullous Dermatitis

Only 1 case, a 17-year-old patient, of linear IgA bullous dermatitis has recently been described [37]. She was effectively treated with dapsone 125 mg per day, but after 3 years, without any interruption or reduction of the drug, she presented a flare mainly in the axillae with a number of blisters. Based on the hypothesis that sweating may explain the appearance of lesions in the axillae, the authors decided to perform botulinum toxin injections into one axilla. The treatment with 50 U of BoNT-A was effective after 3 weeks, and so it was performed in the other axilla with 6 months of remission. The patient requested a new treatment due to her great satisfaction.

Genodermatoses

Epidermolysis Bullosa Simplex, Weber-Cockayne Type

The Weber-Cockayne type of epidermolysis bullosa simplex (EBS-WC) is caused by a genetic mutation in the keratin intermediate filaments 5 and 14 in the basal layer of the epidermis that lead to a recurrent blistering eruption after frictional trauma, especially on the hands and feet [38]. During the summer months and in warm climates patients observe a worsening, probably due to hyperhidrosis; these findings supported a series of reports [39, 40] and then a double-blind, placebo-controlled crossover study of the application of aluminum chloride 20%, well-known for its antiperspirant properties, in 23 subjects with EBS-WC, which failed to show any difference between the treated and placebo groups [41]. In 2009, Abitbol and Zhou [42] decided to treat with BoNT-A a 43-year-old woman affected by EBS-

Table 2. Botulinum toxin type A (BoNT-A) injection therapy in Hailey-Hailey disease

First author [Ref.], year	<i>n</i>	Sites	BoNT-A doses	Follow-up	Results
Lapiere [26], 2000	1	Axillae	25 U, 50 U of per axilla after 6 months	4 months at time of publication	Complete remission
Konrad [27], 2001	1	Submammary	BoNT-A on both sides of the sub-mammary region; 4 days later a limited area of 25 cm ² on each side was treated with dermabrasion or erbium:YAG laser	12 months	BoNT-A induced remission without abrasion for at least 12 months
Kang [28], 2002	1	Groin, axillae	100 U for each inguinal fold	6 months	Improvement
Koeyers [29], 2008	6	NA	n.a.	n.a.	n.a.
Bessa [24], 2010	2	Groin, axillae	125 U of BoNT-A for each axilla and inguinal fold	1 month at time of publication	
Lopez-Ferrer [30], 2012	3	Axillae Groin, breast, axilla Axillae and groin	80 U/axilla 200 U total 200 U total	5 months	All patients improved but needed at least one retreatment after 1–3 months
Bedi [31], 2015	1	Intergluteal	100 U every 3 months for 9 months	Not reported	Remission with injections every 6 months and topical tacrolimus 3–4 weekly
Ho [32], 2015	1	Axillae	Not reported	3 months	Improvement
n.a., not available.					

WC who presented with multiple blisters, erosions, and crusts on the bottom of both feet. One foot was treated with 100 U of BoNT-A and the other with normal saline solution; the authors followed up the patient for 3 months, observing a decrease in blister formation on the treated foot. This case report remains actually the unique report of BoNT-A injection therapy in EBS, but the promising result can stimulate further studies and applications.

Darier Disease

The first report of the use of BoNT-A as an adjuvant therapy in Darier disease dates back to 2007, when Kontochristopoulos et al. [43] successfully treated the submammary areas of a 59-year-old patient. Another case in 2008 confirmed the usefulness of sweating reduction in the intertriginous area in a young patient with severe involvement of the anogenital area [44]. She was treated with acitretin 10 mg per day and with antimicrobial and antifungal drugs for the coexisting infection, but her poor quality of life and discomfort remained significant. BoNT-A injections were performed (40 U into each inguinal fold and 20 U into each anal fold) with a considerable improvement after 3 weeks both in symptoms and in clinical lesions.

Pachyonychia Congenita

Pachyonychia congenita (PC) is a rare genodermatosis; affected patients show hypertrophic nails and hyperkeratosis on the soles (keratoderma) that are extremely painful. High ambient temperature, summer, and sweating worsen this condition until disability [45]. In 2006, based on this evidence, Swartling and Vahlquist [46] injected BoNT-A in 3 patients affected by PC; the authors reported not only the anhidrotic effect, but also a great improvement in pain and discomfort, as acitretin therapy was stopped. One patient abandoned wheelchair use. The promising experience of Swartling and Vahlquist led the same authors to an interesting retrospective evaluation of the effects of BoNT-A injections in 14 patients with EBS and PC with foot blisters and painful callosities [47]. They observed analogous results in improvement of blisters and pain; the hypothesis that explains these effects was that BoNT-A can affect nociceptive C-fibers in the skin via inhibition of neuropeptide release from sensory nerve axons and also inhibits the neurogenic inflammation [48]. Recently, 2 new cases of PC treated with BoNT-A injection have been described [49]. It is interesting that 1 of these patients was treated for 5 years, every 6 months, without a loss of response, so she could stop acitretin and planned a pregnancy.

Table 3. Suppurative hidradenitis and botulinum toxin type A (BoNT-A) injection therapy

First author [Ref.], year	Type of study	<i>n</i>	BoNT-A doses	Follow-up	Retreatment	Results
O'Reilly [47], 2005	Case report	1	250 U Dysport/axilla	10 months	No	Complete remission
Feito-Rodriguez [48], 2009	Case report	1	40 U total dose (inguinal folds)	6 months	Yes	Complete remission
Khoo [49], 2014	Case report	3, but only 1 described	50 U/axilla	3 years	Yes (3 other times)	Complete remission

Hidradenitis Suppurativa

Hidradenitis suppurativa (HS; or acne inversa or Verneuil disease) is an inflammatory, debilitating skin disease with multiple flare-ups. It affects the apocrine gland-bearing areas with boils, sinus tracts, fistulae, and scarring. Patients afflicted by HS have severe discomfort and psychosocial costs [50]. Although suppurative hidradenitis may not be primarily a disease of the apocrine glands, the glands remain a potential therapeutic target. In 2005, the first case of HS of the axillae was described in a young woman successfully treated with BoNT-A with 10 months of complete absence of symptoms [51]. In 2009, Feito-Rodriguez et al. [52] also reported the case of a prepubertal HS in a 7-year-old girl. The disease was recalcitrant to all topical and systemic drugs, with partial remission and early relapse after stopping any therapy. Forty units of BoNT-A was injected on each side with a complete remission until 6 months later. The reoccurrence responded to a similar second treatment. Khoo and Burova confirmed the efficacy of BoNT treatment in HS in 3 cases [53]. One of them, a 46-year-old woman, was affected by a Hurley stage II HS and hyperhidrosis involving axillae and groin, recalcitrant to conventional therapies and also previously treated with surgical drainage of abscesses. Over the course of 3 years, she received 4 treatments with 50 U of BoNT-A (100 U dissolved in 4 mL of 0.9% NaCl solution) per treatment administered to each axilla. She showed good clinical response within 3 months of her first treatment, and after the second treatment, she experienced a complete remission. We also experienced the potential therapeutic role of BoNT-A in HS treating 2 cases [54]. The exact mechanism by which BoNT-A affects the disease process in HS is unclear. It is widely known that a moist environment in folds, especially in the axilla and groin, provides ideal conditions for the flourishing of bacteria and is a precipitating factor of HS. The effect of BoNT-A on sweat production can reduce the population of skin flora and its potential proinflammatory effect. HS was formerly

considered to be primarily a disorder of the apocrine sweat glands, but recent studies have shown that we have to consider HS as a disorder of follicular epithelium [55]. In fact, a second hypothesis on the therapeutic effect shown by BoNT-A is that it prevents the rupture and spread of follicular material through the dermis, which would usually promote inflammation and sinus tract formation [51]. Table 3 collects all the studies conducted on the BoNT-A application in HS.

Aquagenic Keratoderma

Aquagenic keratoderma (AKD) is a rare condition that causes a translucent whitish and thickening pebbly of the palms and soles after immersion in water. Patients suffering from AKD report tightness, pruritus, and mild pain [56]. Three cases of AKD treated with BoNT-A injections have been published. The first one, in 2005, described a 35-year-old woman who presented with a 2-year history of discomfort in her hands after 5 min of contact with water [57]. She also suffered from axillary and palmar hyperhidrosis; after an unsuccessful treatment with aluminum chloride and the involvement of the feet, she was treated with BoNT-A on the palms with a great improvement that lasted 5 months. The other 2 cases, both in 2010, had a good response to BoNT-A therapy [58, 59]. Bagazgoitia et al. [59] suggested that the excellent response to botulinum toxin in the patients was probably due to an involvement of eccrine glands and sweat in the pathogenesis of AKD.

Alopecia

Alopecia Areata

Alopecia areata (AA) is a common dermatosis that causes patches of nonscarring hair loss on the scalp or eyebrows, beard, and less frequently on other skin areas [60, 61]. The autoimmune hypothesis is the most exam-

ined, but the pathophysiology of AA appears complex [60]; in 1994, Paus et al. [61] demonstrated that substance P (SP) may play a role in the neural control of hair growth. They suggested an interesting interaction in epithelial-mesenchymal-neuroectodermal system of the hair follicle. Based on these data, Rossi et al. [60] showed decreased calcitonin gene-related peptide (CGRP) and SP levels in the scalp biopsy of patients affected by AA and postulated that this may explain the reduced basal microvascular blood flow observed in patients with alopecia. The first case of alopecia cured with BoNT-A injections was a 34-year-old woman affected by a cephalalgic alopecia, a severe form of headache with a burning pain of the scalp, allodynia, and hair loss in involving areas, similar to AA [62]. The patient was refractory to all attempted therapies with an increasing, disabling pain; therefore BoNT-A was injected into procerus, corrugator, frontalis, temporalis, splenius capitis, occipitalis, and trapezius muscles (100 U in total). The beneficial effect started 10 days after the injection and lasted for 6 weeks; 3 months later, a second treatment was assessed with the same doses. The patient experienced a complete remission of pain for 60 days and had a significant hair regrowth. A novel treatment with BoNT-A was necessary after 8 weeks with similar efficacy. Cutrer et al. [63] described other 3 similar cases in 2010. Irimia et al. [64] in 2013 confirmed the efficacy of BoNT therapy for cephalalgic alopecia with another case treated with onabotulinum toxin A. The disease and the efficacy of BoNT-A treatment suggest a common pathophysiology for both phenomena. Biopsy specimens from scalp areas in cephalalgic alopecia showed lymphocytic infiltration around the hair bulb and a decreased density of nerve fibers including SP-positive and CGRP-positive fibers. These alterations were reversible after onabotulinum toxin A treatment [63]. In 2010, Cho et al. [65] enrolled 7 patients with AA that received 10 U of BoNT-A intradermal injections on each site monthly for 3 months. The results were discouraging, so the authors concluded that BoNT-A therapy did not affect hair growth in AA, but they did not exclude that using BoNT-A at the right stage and severity can lead to an improvement of AA.

Androgenetic Alopecia

This form of alopecia is still a challenging disease that affects both genders and is characterized by hair loss in a specific pattern of the scalp [66]. In 2010, 50 male subjects (19–57 years old) with Norwood/Hamilton ratings II–IV were enrolled and treated with 150 U of Botox® (5 U per 0.1 mL saline) into the muscles surrounding the scalp,

including frontalis, temporalis, periauricular, and occipitalis muscles for a total of 30 injection sites. The primary outcome measure was a change in hair count in a fixed 2-cm area and the secondary outcome was hair loss, measured with the count of loose hair on the pillow [67]. Forty subjects completed the study period with a statistically significant increase in hair counts (18%) at week 48. The hypothesis that sustains the use of BoNT-A in androgenetic alopecia links with the low-oxygen environment in areas of the scalp with sparse hair growth. Blood flow may therefore be a primary determinant in follicular health, and Goldman et al. [68] demonstrated a microvascular insufficiency to the regions of the scalp that lose hair in male pattern baldness. BoNT-A injected into the scalp reduces pressure on the perforating vasculature with an increasing blood flow and oxygen concentration. Therefore, the enzymatic conversion of testosterone to dihydrotestosterone is oxygen dependent, so where oxygen rate is low, this conversion is favored; whereas in high-oxygen environments, more testosterone is converted to estradiol.

Psoriasis

The role of the nervous system in psoriasis has been postulated after a number of studies that demonstrated a high nerve fiber concentration in psoriatic skin and an increased level of sensory nerve-derived CGRP and SP. Therefore, the clinical observation that psoriasis undergoes remission following loss of innervation, nerve function or nervous system injury, supports this hypothesis [69]. BoNT-A inhibits nerve-derived release of CGRP and SP, and this probably explains the subjective clinical observation of disease improvement in inverse psoriasis following BoNT-A administration by Zanchi et al. [70]. Ward et al. [69] demonstrated, using adult KC-Tie2 mouse (a murine model of psoriasiform dermatitis) that the intradermal injections of BoNT-A lead to a significant improvement versus placebo in acanthosis and a reduction of cutaneous lymphocyte infiltration. However, clinical reports and observational study published are few and not placebo-controlled. Zanchi et al. [70] reported a good response to the BoNT-A treatment in 15 patients with inverse psoriasis, but the outcomes were evaluated with patient self-assessment (VAS scale for itch and pain) and a photographic evaluation of erythema and infiltration. For this reason, Chroni et al. [71] raised several criticism in the study such as the absence of a quantitative measure in order to estimate the improvement (PASI

Table 4. Psoriasis and botulinum toxin type A (BoNT-A) injection therapy

First author [Ref.], year	Type of study	n (type of psoriasis)	BoNT-A doses	Retreatment	Follow-up	Results
Gilbert [68], 2014	Case report	1 (plaque psoriasis)	30 U of abobotulinum toxin A on a plaque on the buttock	Not reported	8 months	Remission; relapse after 8 months
Zanchi [66], 2008	Observational, no RCT	15 (inverse psoriasis)	50–100 U	Not reported	12 weeks	Improvement in VAS scale score; photographic assessment with improvement of erythema, infiltration (87%)

RCT, randomized clinical trial; VAS, Visual Analogue Scale.

score, for example) or a histological evaluation prior and post treatment. The Authors hypothesized beneficial effects of BoNT-A in reducing local sweating in folds, such as HHD (or familial benign chronic pemphigus), where the efficiency of BoNT-A is hypothetically due to a sweating reduction [27, 28, 30, 33, 36]. However, the patients reported also a reduction in pain and itch, probably due to the capability of BoNT-A to block algogenic neuropeptide liberation [72]. Table 4 schematizes the cases reviewed.

Notalgia Paresthetica

Notalgia paresthetica (NP) is a challenge-to-treat condition that is considered a sensory mononeuropathy of unknown origin and that usually affects the skin of the dorsal segments D2–D6. Patients reported pruritus, pain, paresthesia, hypo- and/or hyperesthesia, and burning. NP is clinically defined by a brownish patch in the affected area that is constantly scratched; NP mainly occurs in older patients or is linked with musculoskeletal compression of spinal nerves [73]. The first 2 cases of NP treated with botulinum toxin were described in 2007 [74]. In 2010, Wallengren and Bartosik [75] treated 6 patients affected by NP or neuropathic pruritus with a small improvement. Until now, there has been only 1 double-blind randomized clinical trial concerning the use of BoNT-A as a therapy for NP [76]. In this study, published in 2014, Maari et al. [76] enrolled 20 patients resistant to topical therapies; patients were randomized to either BoNT-A (onabotulinum toxin A) or saline alone (placebo). Improvement in pruritus was evaluated with the VAS scale for pruritus. Patients in the BoNT-A group received injections of 0.1 mL (50 U/mL) for every 1–2 cm² of hyperpigmented area; if there was no hyperpigmentation, the pruritic area as delimited by the patient (maxi-

mum intradermal dose of 200 U BoNT-A). Patients in the placebo group received a corresponding volume of saline. Patients who received placebo at baseline received BoNT-A at week 12, and all patients continued the study until week 24. Statistical analysis revealed no significant mean difference in pruritus VAS between patients treated with BoNT-A and those that received placebo 8 weeks after the treatment. There was no significant difference between the groups also in hyperpigmentation or investigator and patient global efficacy. Table 5 collects all the cases previously described.

Facial Erythema and Flushing

Several recent reports demonstrate the possible action of botulinum toxin for facial erythema and flushing. After some exciting case reports [77, 78] and equally discouraging results [79, 80, 81], in 2011 Odo et al. [82] realized a numerous enrollment of 60 women affected by menopausal hot flushing and treated the affected area (scalp, face, neck, and chest) with a total of 500 U of abobotulinum toxin A, diluted in 3.2 mL of saline solution, and applied intradermally as a 6.2-U injection at each selected point in the skin. For the control group, saline solution was used at the same volume of 0.04 mL per injection point. The objective of this study was to reduce the discomfort of menopausal hot flashes. The Minor test was used for detect the perspiration areas and patients kept a diary with all the information related to flushing, intensity, number of episodes, area affected. At the 180-day follow-up, patients reported a recurrence of excessive perspiration, but the symptoms were less severe than before treatment. In the control group, there was no significant difference in mean intensity of sweating or in the mean number of hot flashes. In the patients in the study group, no staining was detected with the

Table 5. Studies concerning the use of botulinum toxin type A (BoNT-A) in notalgia paresthetica

First author [Ref.], year	Type of study	n	BoNT-A doses	Retreatment	Follow-up	Results
Maari [72], 2014	RCT vs. placebo double-blind	20	max 200 U	No	12 weeks, then placebo arm shifted to BoNT-A; total 24 weeks	No significant difference for pruritus (VAS) and hyperpigmentation
Pérez-Pérez [73], 2014	Retrospective, case series	5	48–56 U	No	18 months	2 worsening pruritus, little improvement in other 3 but for only 1 month
Wallengren [71], 2010	Prospective	6	18–100 U	No	18 months	5/6 patients a mean reduction of VAS by 28% at week 6; at 18 months 1 patient had a VAS of 45%, another one was still free from itch
Weinfeld [70], 2007	Case report	2	16–24 U	Yes, 18 months later with 48 U (only 1 patient)	18 months	Improvement (patient self-assessment)

RCT, randomized clinical trial; VAS, Visual Analogue Scale.

starch-iodine test 60 days after treatment at the sites treated with BoNT-A. At 180 days after treatment, symptoms returned to pretreatment levels. Although these results appeared satisfying, the authors admitted several limits: the difficulty to detect and treat well all the skin area involved in hot flushing; the impossibility for patients treated with BoNT-A to distinguish flushing because sweating was reduced or blocked. More recently, Geddoa et al. [83] injected BoNT-A in the neck and/or chest of 22 patients affected by primary flushing in a single-armed, uncontrolled, study. The affected area was marked and divided into 1-cm squares; 2 U of onabotulinum toxin A were injected intracutaneously into each square for a maximum of 100 U. Outcomes were evaluated with DLQI (Dermatology Life Quality Index) questionnaire. Twenty patients (90.9%) reported immediate improvement with almost complete resolution of their flushing, and the remaining 2 patients had a second treatment session to achieve similar results. At 4 weeks' follow-up, the quality of life was significantly improved. Botulinum toxin seems an effective therapy also in refractory erythema and flushing in patients with rosacea, as demonstrated in a report of 2 cases by Park et al. [84]. The state of the art concerning the role of BoNT-A in these diseases is still debatable, and published studies revealed contrasting results in terms of efficacy. It is also true that it is difficult to assess an objective measure of a transient, subjective sign such as erythema and flushing. Not less relevant, the studies conducted up to date have a very short follow-up with minimal long-term data on

efficacy and safety [85–87]. Table 6 resumes published studies concerning flushing and erythema treated with botulinum toxin.

Oily Skin

In 2008, Shah [87] published a retrospective analysis of 20 patients in order to evaluate the safety profile and subjective efficacy of intradermal BoNT-A in facial ("T-zone") pore size and sebum production. Patients were satisfied with the improvement in sebum production and the decrease in pores size. These preliminary data, lacking of an objective measurement of sebum production, inspired the prospective study of Rose and Goldberg [87]. The aim of this study was to evaluate the safety and efficacy of intradermal botulinum toxin for the treatment of oily skin in the forehead region; the efficacy was evaluated by 25 subjects with a satisfaction scale and objectively with sebumeter readings at 4 follow-up points and pre- and posttreatment photographs. Each 300-U vial of abobotulinum toxin A was diluted using 3 mL of bacteriostatic saline and was injected intradermally into 10 injection sites of the forehead, and 3–5 U of botulinum toxin were injected at each point (total amount of 30–45 U). The authors observed a significantly lower sebum production, and 91% of patients were satisfied. The mechanism by which intradermal botulinum toxin results in decreased sebum production is not entirely clear because the role of the nervous system and acetylcholine on sebaceous glands is not well defined.

Table 6. Studies concerning the use of botulinum toxin type A (BoNT-A) therapy in facial flushing

First author [Ref.], year	Type of study	n	BoNT doses	Follow-up	Results
Park [80], 2015	Case report	2	3 U in chin and the eyebrow area were injected; after 1 week, 5 U in each cheek and 2 U in chin and the eyebrow area were additionally injected (patient 1) 40–15 U in the first treatment and 5 U in the second treatment for each cheek (patient 2)	1 week to 3 months	Good improvement (photographic assessment)
Bloom [81], 2015	Prospective	25 (15 patients completed the study)	15–45 U of intradermal injections of abobotulinum toxin A into the nasal tip, nasal bridge, and nasal alae	3 months	The treatment resulted in statistically significant improvement in erythema grade at 1, 2, and 3 months after treatment when compared with baseline (3-grade scale of erythema severity on photographic assessment)
Geddoa [79], 2013	Pilot prospective	22	2 U per injection point with maximum dose of 100 U (neck and/or chest)	4 weeks	Twenty patients (90.9%) reported immediate improvement, and the remaining 2 patients had a second treatment session to achieve similar responses; at 4 weeks follow-up significant improvement in quality of life was measured with DLQI score
Odo [78], 2011	RCT	60 women with menopausal hot flushing	500 U abobotulinum toxin A, 6.2 U injection at each selected point in the skin (40 injection points of face, chest, neck, scalp); for the control group, saline solution was used at the same volume of 0.04 mL per injection point	6 months	The symptoms were less severe than before treatment; in the control group, there was no significant difference in mean intensity of sweating or in the mean number of hot flashes
Oh [82], 2011	RCT	15	BoNT-B doses NA; one side of the face was treated with BoNT-B, the other side with saline	8 weeks	Ineffective; mexameter demonstrated significant improvement of erythema at 8 weeks after injections on both sides; the BoNT-B injection side did not show a significant decrease in objective erythema, compared with the control side; subjective satisfaction did not differ between the treated side and the control side
Alexandroff [77], 2006	Case report	2	10 U spaced/hemifacial 1 cm between injections	6 weeks	No improvement was noted 6 weeks after treatment
Kranendonk 2005 [76]	Case report	1	2 U in midcheek region	Not reported	Paralysis of the zygomaticus major; no improvement after 1 week
Yuraitis [75], 2004	Case report	1	A total of 10 U were distributed at 1-cm increments to each cheek in the areas of the most prominent erythema	2 weeks	Marked improvement and high satisfaction

RCT, randomized clinical trial; DLQI, Dermatology Life Quality Index.

Probably the arrector pili muscles and the local muscarinic receptors in the sebaceous gland are targets for neuro-modulatory effects of BoNT. Therefore, for an effective treatment, the injection technique and placement are critical for treating oily skin. A procedure that facilitates the correct placement into the dermis is inserting the needle at a 75° angle and considering the extrusion of toxin from

adjacent pores as an endpoint [87]. Shah et al. [87] also demonstrated a reduction in pore size using a subjective photographic assessment, but this method is not accurate; however, previous studies demonstrated that sebum level strictly correlates with pore size [88]. Further study is needed to determine the optimal injection techniques, doses and applications for oily skin and enlargement of pores.

Raynaud Phenomenon

Raynaud phenomenon (RP) is considered an exaggerated physiological response of blood vessels in the extremities to cold and emotional stress. Classical RP shows 3 phases of color change from pale (vasoconstriction) then cyanotic (ischemic phase) to ultimately red (reactive hyperemia) [89]. RP can be a primary and isolated disorder, or it can anticipate a systemic sclerosis (SSc) or other condition (secondary RP). The advanced stage of the disease causes ulceration of the fingertips and necrosis of the phalanges. These complications are observable in secondary RP (SSc-related), due to the severe vasculopathy, but not in primary RP [89]. In most of the primary RP cases, simple behaviors can control the disease: avoiding cold, minimizing stress, cessation of smoking and caffeine intake, avoiding vasoconstrictive drugs [90]. When lifestyle modifications are insufficient, pharmacological or surgical procedures are needed. Currently, RP is managed with dihydropyridine calcium channel blockers as first line agents, other therapies being topical glyceryl trinitrate, phosphodiesterase 5 inhibitors, a prostacyclin analogue (iloprost), an endothelin receptor antagonist (bosentan) and surgical sympathectomy [90, 91]. The first report of the possible therapeutic role of BoNT-A in 2 patients affected by RP was presented in 2004 [92]. In 2007, Van Beek et al. [93] treated 11 patients with vasospasm associated with a connective tissue disorder. After these encouraging reports, Neumeister et al. [94] published a retrospective review on 19 Raynaud patients injected with BoNT for treatment of ischemic pain of hand digits. The severity of disease and the response to treatment were evaluated with photographic assessment and rate of perfusion with laser Doppler. Each 100-U vial of BoNT-A was diluted in 20 ml of normal saline; 50–100 U were injected into the palm around the neurovascular bundles at the level of the metacarpophalangeal joint in each hand. Sixteen of 19 patients experienced a rapid resolution of pain, and 13 reported an immediate improvement; the other 3 patients reported a more gradual reduction over 1–2 months. Also chronic ulcers on the fingers healed within 60 days. The only completed randomized controlled trial pilot of BoNT-A use in RP was undertaken by Jenkins et al. [95]. Ten patients were randomized to receive BoNT-A injections into either hand, while the contralateral hand was injected with saline as a control. The primary outcome in this study was digital pulp temperature. The authors reported a significant increase in digital pulp temperatures of the hands treated with BoNT 6 weeks after treatment from baseline as compared with

the control hands. The sites of BoNT-A injection were also not well described across studies; substantially, the targets were neurovascular bundles of digits and/or the superficial palmar arch. Fregene et al. [96] compared different injection sites (wrist, neurovascular bundles of digits, and the distal part of the metacarpus) and found no significant difference in efficacy outcome. Therefore, in some studies the patients enrolled are not well identified as a primary or secondary RP. The prospective case series study by Motegi et al. [97] is unique in that it enrolled 10 patients affected by RP concomitant to SSc and treated all of them with BoNT-A. All studies, summarized in Table 6, enrolled only a few patients and are totally lacking a standardization injection protocol and outcomes. Therefore, some authors did not declare well the coexistence of an SSc or other diseases with the RP, creating a bias in the evaluation of BoNT-A efficacy [98–101]. Table 7 illustrates the aspects of these studies.

Pompholyx

Pompholyx or dyshidrotic eczema is a common relapsing vesicular-bullous disease of the palm and/or soles. The pathogenesis of this condition is still unresolved, but it is currently considered a manifestation of atopy or contact dermatitis [102]. The most important provoking factors are wet works, sweating, and occlusion [103]. Patients report pain, itching, burning sensation and discomfort in wearing gloves or shoes; bacterial infection and/or mycosis are common. Swartling et al. [102] observed an improvement in hand eczema in patients treated with BoNT-A for palmar hyperhidrosis. In 2002, they published the results of a trial including 10 patients with bilateral vesicular hand dermatitis; one hand was treated with BoNT-A injections (100 U Botox® diluted in 1 mL of saline), and the opposite hand was used as a control at the follow-up. Seven of 10 patients reported a good or very good effect of the treatment. Wollina and Karamfilov [104] performed a prospective side-by-side controlled clinical pilot study using topical corticosteroids on both hands in combination with intracutaneous injections of 100 U of BoNT-A (Botox®, diluted in 2 mL of saline) on the more severely affected hand in 6 patients. The authors observed a rapid improvement in pruritus and vesiculation in the hand treated with combination therapy and explained the efficacy of BoNT-A in pompholyx not only with its anhidrotic effect, but also in its inhibition of SP. In 2007, a report described 2 cases of palmar pompholyx that improved after BoNT-A therapy

Table 7. Studies concerning the use of botulinum toxin type A (BoNT-A) injection therapy in Raynaud disease and phenomenon

First author [Ref.], year	Type of study	<i>n</i>	BoNT-A doses/hand	Follow-up	Retreatment	Results
Motegi [93], 2016	Prospective, case series	10	10 U/finger	16 weeks	No	Improved (pain, DU, skin temperature)
Uppal [94], 2014	Prospective	20	100 U	6 months	No	Improved (pain with VAS, DU)
Jenkins [91], 2013	RCT pilot; double-blind; placebo	8	40 U	–	No	Increase in digital pulp temperature
Smith [95], 2012	Case report	1	100 U	–	No	Patient reported improvement in pain and DU
Neumeister [96], 2010 Neumeister [90], 2009	Retrospective case series	33	50 U	1–6 years	Yes (21%)	100% of DU healed, relief in 85% of patients
Fregene [92], 2009	Retrospective case series	26	20–100 U	18 months	Yes (20%)	48% of DU healed, 35% pain reduction (VAS)
Kossintseva [97], 2008	Case report	1	100 U	12 months	No	Pain decreased, DU not reported
Van Beek [89], 2007	Retrospective case series	11	50–200 U	9.6 months	Yes (45%)	100% decrease in pain (VAS), 82% of DU healed
Sycha [88], 2004	Pilot to RCT, case report	2	12–300 U	–	No	37% pain reduced in 1 patient (VAS), other unknown

RCT, randomized controlled trial; DU, digital ulcer; VAS, Visual Analogue Scale.

Table 8. Studies concerning the use of botulinum toxin type A (BoNT-A) in hand pompholyx

First author [Ref.], year	Type of study	<i>n</i>	BoNT-A doses/hand	Follow-up	Retreatment	Results
Kontochristopoulos [101], 2007	Case reports	2	4.0 mL saline in 100 U BoNT-A; 100 U/hand	8 weeks	No	Improvement
Swartling [98], 2002	Prospective	10	1.0 mL saline in 100 U BoNT-A; mean of 162 U/hand	28–59 days	No	7 of 10 patients reported a good result; improving in VAS for itching and disease activity score
Wollina [100], 2002	Prospective; side-by-side monotherapy with topical steroid vs. adjuvant BoNT-A injection	6	2.0 mL saline in 100 U BoNT-A	8 weeks	No	Six of 6 hands treated with topical steroids in combination with BoNT-A showed improvement; BoNT-A showed a more rapid release from itching than steroids alone

VAS, Visual Analogue Scale.

for palmar hyperhidrosis [105]. It is interesting to note the lack of studies on the use of BoNT-A in plantar eczema, maybe for the same reasons that restrict its use in plantar hyperhidrosis (pain, width of the plantar area, need of more units and related more cost, less efficacy). Moreover, the dilutions chosen by the authors are different from the regimen for palmar hyperhidrosis, but this is not clearly explained. No placebo-controlled trial has been published. The studies are resumed in Table 8.

Chromhidrosis and Bromhidrosis

Chromhidrosis is a rare condition characterized by the secretion of pigmented sweat. The color can be yellow, green, blue, or black; the disease typically affects the face or axillae. It is easy to understand the strong impact on patient's quality of life [106]. If this condition is a primary disorder of the apocrine or the eccrine glands is still debated. Wu et al. [106] proposed an apocrine-related

Table 9. Case reports of chromhidrosis treated with botulinum toxin type A (BoNT-A) injections

First author [Ref.], year	Type of study	n	BoNT-A doses	Follow-up	Retreatment	Results
Tato [105], 2012	Case report	1	5 mL of saline in 100 U BoNT-A 10 U on each cheek	4 months	No	Improvement but no complete remission
Beer [104], 2010	Case report	1	4 mL of saline in 100 U BoNT-A 50 U per axillae	Not reported	Yes, twice a year with same doses and results	Complete remission; no side effects
Wu [102], 2005	Case report	1	2 mL of saline in 100 U BoNT-A 10 U intradermally on the right cheek	19 weeks	No	Complete remission; no side effects
Matarasso [103], 2005	Case report	1	2 mL of saline in 100 U BoNT-A 15 U intradermal on each cheek (total of 30 U)	4 months	No	Complete remission; no side effects

pathogenesis after their first case successfully treated with BoNT-A, even though apocrine glands are traditionally thought to be unresponsive to cholinergic stimulation and so to the botulinum toxin. In contrast, Matarasso [107] considered chromhidrosis an eccrine-related disease exactly for the good response to BoNT-A treatment. A 62-year-old woman affected by an axillary chromhidrosis was treated by Beer and Oakley [108] with a complete remission; the patient's satisfaction was so high that she returned for a retreatment periodically, twice a year. The BoNT-A treatment was only partially satisfying in the patient with cheek chromhidrosis treated by Tato et al. [109], probably due to the greater dilution of the toxin. The efficacy of BoNT-A in the treatment of this uncommon but highly embarrassing disease did not explain its pathogenesis but is currently a great possibility for the affected patients. The treatment of the cheek area needs more standardization regarding dilution and doses in order to achieve the best results without the risk of injections in the eye area. Table 9 resumes all the case reports.

Axillary bromhidrosis is a condition in which body odor is induced by the interaction between apocrine gland secretions and bacteria [110]. In 2012, He et al. [110] enrolled 67 patients with axillary bromhidrosis. Each axilla was injected with 50 U of BoNT-A, and the follow-up was done every month. The authors reported that the malodor was eliminated in 73.1% (49/67) of patients and that the treatment with BoNT-A was effective in patients with a strict correlation between sweating and malodor. Therefore, a close positive correlation between malodor and sweating is the major indication for BoNT-A treatment.

Foul genital odor is another distressing problem in both men and women, with a great impact on the quality of life. The etiology of genital odor is frequently due to

bacterial infection of genital skin or vaginal mucosa, but in some cases the reason is the interaction between local sweat and certain types of bacteria. Lee et al. [111] described a unique case of a female patient with a several years' history of foul genital odor treated unsuccessfully with antibacterial soaps, perfume and antimicrobial agents. There were no signs of infection in the vagina or cervix. A BoNT-A treatment with injections in 40 different sites (2.5 mU/0.1 mL per site) of the genital hair-bearing area led to a significant decrease in the odor. The efficacy was maintained for 9 months.

Eccrine Nevus

Congenital eccrine nevus (EN) is a rare skin hamartoma characterized histologically by increased numbers and/or size of the eccrine glands, without vascular proliferation. This last aspect distinguishes the EN from other conditions such as angiomatous eccrine hamartoma [112]. Clinically, EN appears in most cases on the forearms without skin abnormalities but with a localized area of hyperhidrosis [113]. The area involved and the hyperhidrosis entity influence the therapeutic decision: topical agents or surgical excision is the most common treatment. Honeyman et al. [114] reported a case of congenital EN of the right wrist in a 12-year-old girl resistant to topical antiperspirant agents; surgical excision was discarded due to the size of the lesion and the anatomical site. The hyperhidrosis interfered with social and scholastic activities. The authors decided to inject BoNT-A (diluted in 4 mL of saline solution 0.9%, but the authors did not specify the total amount of toxin) with 5 U per point, at intervals of 0.5–1 cm. The authors did not specify the timing of the first response to BoNT-A treatment, but declared

Table 10. Eccrine hamartomas treated with botulinum toxin type A (BoNT-A) injections

First author [Ref.], year	Type of study	<i>n</i>	BoNT-A doses	Follow-up	Retreatment	Results
Honeyman [110], 2008	Case report	1	BoNT-A, dilution in 4 mL of saline, 5 U per injection; total amount not specified	1 year	Not reported	Improvement
Lera [108], 2015	Case report	1	100 U BoNT-A in 2.5 mL of saline, 2 U per injection	9 months	Yes	Improvement
Nygaard [111], 2015	Case report	1	100 U BoNT-A (dilution not specified)	1 year	Not reported	Improvement

Table 11. Studies concerning the treatment of postherpetic neuralgia with botulinum toxin type A (BoNT-A)

First author [Ref.]	Type of study	<i>n</i>	BoNT-A doses	Follow-up	Retreatment	Results
Moon [117], 2016	Case report	2	50 U BoNT-A and bupivacaine 0.1% injected under ultrasound guide in brachial plexus	5 months	No	VAS for pain decreased from 8 to 2–3
Disen [114], 2015	Case report (ophthalmic)	1	100 U of BoNT-A in the orbital region (subcutaneous)	6 months	No	VAS for pain decreased from 8–9 to 2–3
Apalla [115], 2013	Randomized, double-blind, placebo-controlled trial	29 (4 postherpetic)	20–190 U of BoNT-A intradermally	16 weeks	No	VAS decreasing
Xiao [113], 2010	Randomized, double-blind, placebo-controlled trial	60	5 U/mL of BoNT-A vs. 0.5% of lidocaine vs. 0.9% of saline	3 months	No	Decrease in VAS score and improving in sleep hours superior to control group
Sotiriou [112], 2009	Case reports	3	100 U of BoNT-A in 4 mL of saline; subcutaneous in chessboard pattern	12 weeks	No	Decrease in VAS score
Liu [116], 2006	Case report	1	100 U of BoNT-A injected in a fanning pattern	9 months	No	VAS pain reduction from 10 to 1

VAS, Visual Analogue Scale.

Table 12. Off-label uses of botulinum toxin in dermatology

Keloids and hypertrophic scars
 Hailey-Hailey disease
 Linear IgA-bullous dermatosis
 Genodermatoses
 Hidradenitis suppurativa
 Psoriasis
 Aquagenic keratoderma
 Alopecia
 Notalgia paresthetica
 Facial erythema and flushing
 Oily skin
 Raynaud phenomenon
 Pompholyx
 Chromhidrosis and bromhidrosis
 Eccrine nevus
 Postherpetic neuralgia

that 1 year later they observed a significant decrease in sweat episodes to once a month, and an improvement in our patient's quality of life. In 2015, Lera et al. [112] treated a patient with EN on the forearm; the patient had a poor quality of life with a hyperhidrosis disease severity scale (HDSS) score of 3 (severe). BoNT-A (a total of 100 IU) was reconstituted with 2.5 mL of 0.9% sterile saline solution (each injection of 2 U) and injected into the area shown by the Minor iodine test. The patient noticed a reduction in perspiration 48 h after the procedure with maximum response at week 3. The HDSS score decreased to 1 (mild hyperhidrosis). After 9 months, the BoNT-A treatment was repeated because of a relapse in perspiration. BoNT-A injection therapy has proved to be effective also in the eccrine angiomatous hamartoma [115]. Despite the rarity of the condition, it is easy to understand

the importance of a valid therapeutic alternative for these patients. Table 10 describes the 3 cases reported in the literature.

Postherpetic Neuralgia

The most common complication of herpes zoster is postherpetic neuralgia, a chronic and debilitating pain that is very challenging to treat. Treatment approaches include nonsteroidal anti-inflammatory drugs, gabapentin, opioids, and tricyclic antidepressants as well as topical anesthetics [116], but pain can be resistant to all of these drugs. An interesting randomized clinical trial was conducted by Xiao et al. [117] in 2010 on 60 subjects affected by postherpetic neuralgia. The authors compared the analgesic effect of BoNT-A with lidocaine and placebo (saline). In the treated group, patients reported a decrease in VAS pain that was more significant than that in the control groups. It is interesting to note that for this indication BoNT-A is administered not only subcutaneously [118] but also intradermally [119], with a chessboard [120] or fanning [121] pattern or under ultrasound guidance [122]. The injection of botulinum toxin may reduce various substances that sensitize nociceptors [120], and its analgesic potential is one of the most important opportunities for neuropathic chronic pain (Table 11).

Conclusions

This review emphasizes the great potential of the use of BoNT-A in a large number of heterogeneous dermatological diseases (Table 12). Currently, we do not know all the molecular and pathophysiological mechanisms underlying the therapeutic effects of this drug. From a clinical

point of view, it is evident that many of the diseases that affect the folds (inverse psoriasis, HHD, HS) can improve after injection of botulinum toxin probably owing to its anhidrotic effect reducing bacterial contamination and maceration. Further studies should investigate the role of BoNT-A in the regulation of neuropeptides and the link with the neuroimmune system in order to better understand its therapeutic potential. The limits of the wide application of BoNT-A are substantially restricted by its high cost, since the safety profile is well established and patients tolerate the injections well. Most of these off-label uses of botulinum toxin are for chronic diseases; how long can we use BoNT-A injection therapy without risks or sequelae? Is tachyphylaxis possible? What we know is that botulinum toxin has an immunogenic potential; this can lead to the production of antibodies, neutralizing or not. Many factors can influence the onset of immunogenicity: product factors, toxin components, and protein load, but also treatment-related factors [122]. Botulinum neurotoxin immunogenicity may be related to the dose that is injected. One study has reported that patients who develop neutralizing antibodies require higher and more frequent doses to maintain comparable levels of treatment effectiveness (tachyphylaxis) [123]. The frequency of injection can be related to immunogenicity, so it is reasonable to extend the injection intervals, balancing the expected duration of the clinical effect and the risk for neutralizing antibody development. Finally, a consensus on the dose regimen for each indication and well-defined injection techniques for standardization of all the therapeutic protocols are desirable.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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