Chapter

The Non-Cosmetic Dermatological Use of Botulinum Neurotoxin

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Abstract

Botulinum neurotoxin injections are currently the most popular non-surgical cosmetic therapy for treating hyperdynamic lines and rebalancing face muscles all over the world. However, there is emerging interest in the use of the neuromodulator for the treatment of non-cosmetic clinical conditions. The present evidence supporting the use of Botulinum toxin in the treatment of acne and oily skin, rosacea, alopecia areata and androgenic alopecia, scar prevention and therapy, postherpetic neuralgia, hyperhidrosis, and disorders exacerbated by sweating is discussed in this chapter. Case reports and a few randomized controlled trials are used to support the use of Botulinum toxin in several of these illnesses. Nonetheless, the therapeutic application of Botulinum toxin in various skin conditions linked with discomfort, inflammation, and hyperhidrosis has a lot of promise.

Keywords: botulinum neurotoxin, rosacea, acne vulgaris, oily skin, hypertrophic scars, keloids, postherpetic neuralgia, idiopathic hyperhidrosis, genodermatoses, psoriasis

1. Introduction

Several serotypes of Botulinum neurotoxin (BoNT) are produced by the bacterium Clostridium botulinum, including BoNT-A, B, C, D, E, F and, G [1]. Currently, only BoNT-A and B are commercially available and, the most widely used isoform in both cosmetic and clinical dermatology is BoNT-A.

To date, only four BoNT-A formulations have received FDA approval for several indications. These include OnabotulinumtoxinA, AbobotulinumtoxinA, IncobotulinumtoxinA and, ProatobotulinumtoxinA [2, 3].

Following the initial approval of BoNT-A for glabellar wrinkles by the US Food and Drug administration in 2002, it has been widely used in cosmetic dermatology, for the treatment of hyperdynamic lines and the rebalancing of facial muscles. BoNT-A is currently the leading non-surgical cosmetic procedure, world -wide [2].

The mechanism of action of importance to the aesthetic use of the neurotoxin is chemical denervation and consequent relaxation of skeletal muscle. Post injection, BoNT-A binds to specific presynaptic receptors on the nerve terminal and subsequently becomes internalised into the presynaptic nerve by receptor-mediated endocytosis. Within the nerve terminal, the light and heavy chain of BoNT-A dissociate by the breakage of the disulfide bonds. The light chain, responsible for the action of the neurotoxin, cleaves SNAP-25 docking protein on the internal neuronal

membrane, which plays a key role in the release of acetylcholine during nerve stimulation. Consequently, acetylcholine can no longer be released into the synaptic cleft and muscle stimulation is inhibited until such time as the function of the neuromuscular junction is restored, which normally requires 3 to 6 months [2].

In the past few years, the neuromodulator has gained attention in the field of a clinical dermatology, as an off-label treatment for inflammatory skin diseases and wound healing [4]. The skin is known to interact with the nervous system and there is accumulating evidence that the neurological system has a direct impact on cutaneous inflammation and wound healing. Hence a number of research groups have shown the benefit of BoNT-A injections in acne, rosacea, psoriasis, scar prevention and hypertophic scar treatment, androgenic alopecia and alopecia aerate as well as hyperhidrosis and several conditions exacerbated by sweating [4, 5].

Apart from chemical denervation of cholinergic nerves, other mechanisms have also been postulated as being responsible for the treatment of these conditions includes the inhibition of substance P, glutamate release and calcitonin gene-related peptide (CGRP) and, the suppressions of mast cell activity [6, 7].

This review will address the role of BoNT-A in several non-cosmetic dermatological conditions for which there is current evidence.

2. BoNT-A in oily skin and acne vulgaris

Oily skin is a common dermatological condition reported by many patients, with and without acne. Clinically, the skin appears greasy and unclean with large open pores. Oily skin is troublesome and despite the several topical and systemic treatment options available, it is often difficult to control excessive serum secretion.

The treatment of oily skin with BoNT-A skin was first reported by Shah et al. in 2008 [8]. Twenty subjects with oily skin and large pores were injected intradermally with BoNT-A in the T-zone and evaluated one month post treatment. Photographic evidence of improvement in sebum secretion as well as patient satisfaction was noted in 17 of the 20 subjects [8].

In a prospective study, 25 patients were treated with intradermal injection of BoNT-A on the forehead and followed up for to three months. Sebum production, measured with a sebumeter, revealed a significant reduction in sebum secretion at 1 week and 1, 2 and 3 months after treatment [9]. Furthermore, twenty-one patients (91%) reported that they were satisfied (50–75% improvement) with intradermal botulinum toxin as a treatment for oily skin [9].

A recent split face-controlled study with BoNT-A on one cheek and saline on the other cheek showed a significant decrease in pore size and sebum score at four months in the BoNT-A side as compared to the saline control [10].

Within the sebaceous gland, sebocyte differentiation and sebum secretion are under the control of acetylcholine, since both immature and mature sebocytes express mucarinic acetylcholine receptors. Hence the mechanism of action of BoNT-A is postulated to be due to the inhibition of acetylcholine release into the synaptic cleft, where it normally binds to muscarinic receptors on the postsynaptic membrane [9, 10].

Acne vulgaris, has a prevalence between 82 and 100%, as determined by various studies [11]. Although predominantly believed to be a condition associated with adolescence, it may persist well into adulthood. It is a challenging condition to treat, despite the availability of various topical and systemic options that target the complex pathogenic pathways involved in the development of acne.

The initial step in Acne vulgaris is the formation of the microcomedo [12]. Several factors have been implicated including increased sebum secretion, ductal hypercornification and bacterial colonisation of the pilosebaceous unit by *Cutibacterium acnes* (*C. acnes*).

Hence changes in sebaceous gland function and increased production of sebum are important causative factors in acne [13].

Li et al. showed immunohistochemical and immune-cytofluorescence evidence for the presence of cholinergic receptors in sebaceous glands [14]. Furthermore, the clinical relevance of these findings was assessed by a double-blind, split-face, placebo-controlled study on 20 volunteers. A marked decrease in sebum production was seen in the BoNT-A treated side as compared to the control involunteers with oily skin.[14]

Therefore, the modulation of sebum secretion by blocking the activity of acetylcholine in sebocytes and suppression of the sebaceous gland may have a beneficial action in acne, especially in individuals with oily skin [14, 15]. Although there are no systematic clinical trials in this regard, there are some clinical observations to indicate that BoNT-A reduces acne flares. Patients with Tourette syndrome injected with 20–25 units of BoNT-A into the paranasal facial expression muscles, have shown a clearance of perinasal acne one to two weeks post-treatment with improvement persisting for four months [16]. An interesting outcome of a controlled study on BoNT-A treatment for facial wrinkles was the observation that the rate of acne breakouts in the treatment group was lower than that in the placebo group [17].

An additional benefit of BoNT-A in acne may be due to its inhibition of substance P, since it is known that this inflammatory intermediate stimulates lipogenesis in the sebaceous gland and contributes to the onset and aggravation of inflammation in acne [18].

3. BoNT-A in facial flushing and rosacea

Facial flushing, occurs due to the dilatation of facial capillaries which may be idiopathic or secondary to rosacea. It may be sporadic in nature, initiated by agents that act directly on blood vessels as well as due to stimuli such as alcohol, drugs, food additives, and neurological and hormonal stimuli including menopause. In the majority of cases, the treatment of flushing depends on the management of the underlying cause.

Rosacea, on the other hand, is a chronic inflammatory dermatosis affecting approximately 10% of the population and is characterised by persistent erythema affecting the convexities of the skin of the face [19]. It is often accompanied by telangiectasia and exhibits a poor response to the currently available topical, oral and laser treatment options. Rosacea is classified into four major subtypes; Erythematotelegiectatic, Papulopustular, Phymatous and Ocular rosacea [20]. Erythemto telegiectatic rosacea is associated with persistent erythema and telangiectasia, including episodes of flushing, and is often seen in fair-skinned Caucasian patients. The morphological characteristics of papulopustular rosacea include erythematous papules and pustules on a background of central facial erythema. Phymatous rosacea presents with thickening and hyperplasia of sebaceous glands on the nose. Ocular rosacea, as the name suggests, is associated with blepharo-conjunctivitis and symptoms of dryness, gritty sensation and itching of the eyes [21].

Many rosacea patients have morphological characteristics of more than one subtype of rosacea.

BoNT-A injections have been shown to be of value in the prevention of the erythema and flushing of rosacea. Case studies of two patients treated with intradermal injection

of OnabotulinumtoxinA showed improvement in flushing within 2 weeks and the effect lasted for four months post treatment [22].

A case report involving mesotherapy with BoNT-A for the treatment of refractory erythematotelengiectatic and papulopustular rosacea showed significant reduction in erythema, telangiectasia and flushing [23].

In a larger double-blind split-face study, 24 participants with rosacea were randomised to receive intradermal injection of either BoNT-A or normal saline in both cheeks. On the BoNT-A treated side, the Clinician Erythema Assessment (CEA) score significantly decreased, and the Global Aesthetic Improvement Scale (GAIS) score significantly increased up to 12 weeks post treatment [24].

BoNT-A injections may also be used in combination treatment protocols with energy based devices. In a recent study by Al-Niaimi and co-workers, intradermal BoNT-A injections were used following pulsed dye laser treatments for rosacea. Evaluation of erythema index by 3D camera showed a positive synergistic effect of the treatments with a reduction in grading scores of flushing and erythema [25]. In another study, 16 patients were treated with a Tixel device which causes mechanical disruption of the stratum corneum, followed by topical application of 100iu of Abobotulinumtoxin A. significant improvement of the maxameter sore, clinical erythema assessment (CEA) and patient self-assessment was shown for up to 6 months [26].

To date, the pathogenesis of rosacea has not been fully elucidated. However, several mechanisms have been postulated as being involved including acetylcholine release, imbalance of the innate immune system and the skin microbiota as well as abnormal neurovascular signalling [22]. The release of vasoactive neuropeptides including substance P, calcitonin gene-related peptide and vascular endothelial growth factor as well as cathelicidins are believed to lead to rosacea flares. Cathelicidins are antimicrobial peptides that play a major role in the pathogenesis of rosacea [27]. Recently mast cells have been proposed as being responsible for cathelicidin-induced skin inflammation [6].

Hence the postulated mechanism of BoNT-A in the reduction of Rosacea flares could be due to inhibition of acetylcholine release from peripheral nerves in the cutaneous vasodilator system [22], the inhibition of the vasoactive neuropeptides and cathelicidins as well as the inhibition of mast cell degranulation [6, 27].

4. BoNT-A in alopecia

BoNT-A injections have been studied in the treatment of certain non-scarring alopecias including alopecia areata and androgenic alopecia.

Alopecia aerate (AA) is associated with one or more round, smooth bald patches on the scalp. These may be asymptomatic or associated with trichodynia, a burning sensation in the affected area. It may affect females and males at any age and starts in childhood in half of the cases and before 40 years of age in 80% of cases [28]. Alopecia areata is classified as an auto-immune disorder and characterised on histology by bulbar lymphocytic infiltration around terminal hairs [28]. To date the mainstay of treatment of AA is the use of immunosuppressive treatments, corticosteroid injections and minoxidil [29].

Thus far, the only study in the literature on the use of BoNT-A in AA is by Cho et al. [30] The investigation involved the intradermal injections of 10 U of the neurotoxin in seven patients with AA and the results showed that BoNT-A cannot be used as an alternative treatment for recalcitrant androgenic AA [30]. Nonetheless, since

BoNT-A has an effect on neuro-immunogenic mechanisms, namely the prevention of the release of substance P and calcitonin gene-related peptide, which modulate hair growth [31], further studies concerning the treatment efficacy of BoNT-A for mild to moderate AA are warranted.

Androgenetic alopecia (AGA), is a common type of hair loss in genetic predisposed males and females. It is, in fact, the major causes of progressive hair thinning and affects 50% of females and 80% of the male population [32].

The current hypothesis for the pathophysiology of androgenetic alopecia involves the role of dihydrotestosterone (DHT), a metabolite of testosterone, as the causative factor. DHT is synthesised from testosterone via type II 5-alpha reductase enzyme (5-αR2). DHT accumulates in AGA-prone hair follicles which are sensitive to DHT resulting in the miniaturisation of the hair follicles and ultimately hair thinning, finally culminating in AGA. Consequently, most treatments for AGA target 5 alpha reductase enzyme. The commonly prescribed effective therapy for AGA is Finasteride. The drug reduces serum DHT and scalp tissue DHT by inhibiting 5-αR2. Apart from the genetic predisposition, hypoxia of the scalp is believed to increase the concentrations of DHT by reducing its clearance from the blood [33–35].

Pilot studies [33–35] have shown injections of BoNT-A in various areas of the scalp to be effective in the treatment of AA, resulting in an increase in mean hair count and a reduction in hair loss. The mechanism responsible has been postulated to be due to the relaxation of scalp muscles, thereby relieving scalp tension and resulting in a vasodilator effect. Ultimately the improved perfusion of the scalp along with the enhanced clearance of DHT are responsible for the potential efficacy in the treatment of AGA. A further benefit of the enhanced perfusion is the increased conversion of testosterone to oestradiol, which is known to enhance hair growth.

However, despite the promising results shown in these studies, further investigations such as randomised controlled trials are necessary to establish the benefit of BoNT-A in AGA.

5. Hypertophic scars and keloids

Scars and keloids are a consequence of a dysregulation of the normal wound healing reaction. Wound healing occurs through organised sequential steps of haemostasis, inflammation, proliferation and tissue remodelling. Each of steps of the wound healing cascade is dependent upon several cytokines and growth factors. Interaction among these processes results in the synthesis of collagen over the surface of the wound. On a contrary note, an alteration in the molecular factors, complex network of pro-fibrotic, and anti-fibrotic molecules such as growth factors, proteolytic enzymes, and extracellular matrix proteins may lead to the formation of hypertrophic scars and keloids [36].

Scars have a negative effect on the patient's quality of life as they may impact on the patient both functionally and cosmetically. There are currently various therapeutic approaches in the management of scars including silicone dressings, energy-based devices, surgical excision, cryotherapy and intralesional steroid injections. However, to date, there is not definitive cure and typically combination approaches are employed for the management of scars [37].

The mechanism of action of BoNT-A in the prevention of hypertrophic and keloid scar formation is partially believed to be due to a reduction in fibroblast proliferation and the expression of the inflammatory cytokineTGF-β, one of the main

intermediates responsible for scar formation [38]. The neuromodulator also suppresses the proliferation of fibroblasts in hypertrophic scar tissue [39].

An additional contributing factor to hypertrophic scar and keloid formation is tension on the scar [40]. Hence, BoNT-A may modulate and possibly prevent scar formation by reducing muscle contraction and decreasing skin tension in the scar area.

In a double-blind, split-scar randomised controlled trial in 15 patients with post-thyroidectomy scars. Patients were injected within 10 days of surgery and evaluated at 6 months. Results showed a significant improvement in the BoNT-A treated half of the scar as compared to the saline-treated control [41].

A recent randomised controlled trial in 24 patients with keloids revealed that 5 iu/sq.cm of BoNT-A, injected every 8 weeks for a total of three session, was as effective in softening the keloids and reducing their volume, as intralesional corticosteroids, which are considered the first-line treatment for keloids [42]. Both lesion height and volume were decreased in both cases, however BoNT-A was found to be superior in reducing pain and itch associated with keloids [42]. However, in a prospective uncontrolled study by Gauglitz, patients were injected every 2 months for up to 6 months and the results showed no differences in expression of markers and no regression of keloid tissue was found [43].

Despite the inconsistency in results found in the various studies to date, the role of BoNT-A in the prevention and treatment of hypertrophic scars and keloids does show potential. As such, more structured large- scale double-blind, controlled trials and long-term follow up are warranted to determine the value of BoNT-A in the management and prevention of hypertrophic scars and keloids.

6. Postherpetic neuralgia

Postherpetic neuralgia (PHN) is a very painful conditions which typically occurs post herpes zoster virus infection and can last up to three months, following the initial viral infection. The local neuropathic pain and the sleep disturbances associated with PHN, impacts negatively on the patients quality of life. Conventional treatment approaches include topical agents such as capsaicin and topical anaesthetics as well as nonsteroidal anti-inflammatory drugs, gabapentin and tricyclic antidepressants [44]. However the pain and discomfort may be resistant to all of these drugs.

Xiao et all enrolled 60 patients in a randomised, double-blind, placebo-controlled study whereby patients were divided into three groups; BoNT-A group, saline group and 0.5% lidocaine group. All patients were treated once, with the BoNT-A group receiving a maximum dose of 200iu by intra and subcutaneous injections. The patients were followed up for a period of three months. Of the three groups, the BoNT-A group exhibited the most significant improvement in the Visual Analog Scale (VAS) and sleep quality [45].

In another randomised control trial where 30 patients with PHN were treated with either placebo or a total dose of 200iu BoNT-A, the BoNT-A patients showed a significant reduction in Visual Analog Scale pain sores and which lasted for 16 weeks [46].

The mechanism of pain reduction by BoNT-A is believed to be due to the inhibition of various inflammatory intermediates including calcitonin gene-related peptide, glutamate and substance P.

7. Idiopathic Hyperhydrosis and conditions exacerbated by sweat production

BoNT-A is an established treatment option for primary axillary and focal idiopathic hyperhydrosis and in 2004 OnabotulinumtoxinA received FDA approval for severe primary axillary hyperhidrosis [47, 48]. BoNT-A inhibits the release of acetylcholine from sympathetic nerve fibres that stimulate the eccrine sweat glands and leads to a decrease in sweat production. Several dermatological conditions are exacerbated by sweat and these include Hidradenitis suppurativa, pompholyx, and several genodermatoses including Haily-Haily disease, Darrier disease, Epidermolysis bullosa simplex and Epidemolysis bullosa simples Weber-Cockayne Type, and Pachyonychia Congenita.

Hidradenitis suppurativa (HS) also knows as acne inversa, often starts at puberty and is most active between the ages of 20 and 40 years. It is a a chronic inflammatory condition that affects the apocrine glands-bearing areas in the groin, axillae, and under the breasts. It presents clinically as persistent and recurring painful papules, nodules, abscesses and sinus tracts. The condition is associated with a purulent discharge and culminates in both hypertrophic and atrophic scarring. The pain and psychosocial impact of the disease may be debilitating to HS patients, and many suffer from depression and a negative body image [49].

The first case report of HS of the axillae treated with BoNT-A was in 2005 in a young female who was successfully treated with a single dose of the neurotoxin and remained symptom free for ten months [50].

Thereafter, other case reports confirmed the efficacy of BoNT-A in cases of recalcitrant HS [51–53].

The precise mechanism of action of BoNT-A in HS is unclear but it is believed to be due to the inhibition of sweat production. A moist environment in the inguinal folds and axillae predisposes to maceration and the proliferation of bacteria that precipitate the inflammation and symptoms of HS. Hence the maintenance of a dry environment in the affected areas reduces the population of skin flora and potentially relieves the condition [54].

Pompholyx also known as dyshidrotic eczema is a bullous disease of the palms and soles. The condition is associated with pain, pruritis and discomfort, especially when wearing gloves and shoes. Patients are prone to bacterial and fungal infections and sweat and occlusion are predisposing factors to the condition [55].

Improvement in vesiculation and itch has been shown with intradermal injections of BoNT-A in seven out of ten patients, where one hand was injected with 100 iu of the neurotoxin and the other hand was injected with a saline control. The efficacy of BoNT-A in pompholyx is not solely due to its anhidrotic action but due to its inhibition of substance P [55].

8. Genodermatoses

Certain genodermatoses such as *Hailey-hailey disease (HH), Dariers disease, Epidermolysis Bullosa Simplex (EBS)*, and *Pachyonychia Congenita* (PC) are, in the main, exceedingly painful conditions which have no curative treatments, despite several therapeutic options such as systemic and interventional therapies. These conditions are exacerbated by sweating. Hence BoNT-A has been successfully used for this purpose in several of these disorders. Apart from sweat reduction, the known

modulation of the neurotoxin on pain-related neurotransmitters, contributes to the pain relief and decrease in lesions in these conditions.

Hailey-Hailey (HH) disease also known as Familial Benign Pemphigus is characterised by flaccid blistering lesions and erosions in the intertriginous parts of the body. This condition is exacerbated by sweat and bacterial colonisation, hence the reduction of sweat by BoNT-A has been proven to be of value in the attenuation of the disease. Several case reports using various regimens have shown marked improvement in all cases after injections of BoNT-A [56–58].

Recently a retrospective study of eight patients who were treated with topical BoNT-A post application of the Tixel thermo-mechanical ablative system, showed positive results, with seven patients (87.5%) experiencing good or partial response [59].

A recent systematic review of sixteen publications including a total of 38 patients revealed that of all the cases, only one patient did not have a response while all the other patients had partial or complete remission.

BoNT-A was found to be an encouraging treatment option in recalcitrant HH disease [60].

Darier disease is an autosomal dominant genetic disorder characterised by warty papules in seborrheic and flexural areas. The signs and symptoms of Darier disease vary significantly between individuals. Some patients display minor signs that are asymptomatic whilst others have widespread lesions which may be extremely painful, associated with itch and a distressing malodour.

Case reports on the use of BoNT-A injections have been shown to significantly improve the lesions and symptoms of Dariers disease.

A recent open label 6-month interventional study in three patients with the neurotoxin resulted in a reduction in skin lesions in the affected area and consequently had a positive impact on the patients quality of life [58].

Epidermolysis bullosa simplex(ES) and Epidermolysis bullosa simplex-Weber Cockrayne (EBS-WC) are conditions associated with keratinocyte fragility resulting in bullae, hyperkeratosis and plantar pain. The conditions are exacerbated by warmth and sweat. Several cases of EBS and EBS-WC have been reported in the literature that were successfully managed by BoNT-A. The reduction in pain, blister formation and callosities were found on average, to persist for 3 months [61–63].

Pachionychia congenita (PC) is a rare genetic dermatosis that is characterised by hypertrophic nails and plantar hyperkeratosis. In certain cases, the condition causes severe neuropathic pain, to the extent that some patients are unable to walk and require mobility assistance, such as a wheelchair. The condition is exacerbated by heat and sweat.

In a case series, three patients with PC injected with BoNT-A, experienced decrease in pain and discomfort [64]. A report of two cases treated with plantar injection of BoNT-A for PC, resulted in marked improvement for a duration of six months with no adverse effects or tachyphylaxis [65].

In a recent study, Koren et al. treated five patients with PC and found significant improvement of between 20 and 72% in the PC specific quality of life questionnaire. The duration of effect lasted between 3 and 4 months [66].

9. Psoriasis

Plaque Psoriasis is an inflammatory disease that presents as small to large, well-demarcated dry and red scaly plaques covered with silvery flakes, which may be painful and itchy. Typically, the lower back, trunk, elbows and knees are involved

but it may occur on any part of the body. Inverse psoriasis, sometimes also known as intertriginous psoriasis, is a form of psoriasis that affects skin folds.

Psoriasis is often associated with nail and scalp psoriasis. The condition is associated with multiple comorbidities and markedly diminishes the patients' quality of life.

Whilst topical therapies remain the basis for treating mild psoriasis, currently, biologics that inhibit inflammatory intermediates such as TNF-α and IL-17 are the treatments of choice for moderate to severe disease [67].

Psoriasis is associated with high levels of Calcitonin Gene-related peptide and Substance P and consequently BoNT-A has been shown to be effective in managing both, consequently reducing both itch and pain [68, 69].

G Gonzales et al. treated eight patients with stable and recalcitrant plaque psoriasis, with subcutaneous injections of AbobotulinumtoxinA at a dose of 5 units every square cm. The patients were then evaluated at 2 and 4 weeks after treatment. The outcome was a significant improvement in all patients, 4 weeks after treatment, with no significant side effects [70].

In a split body comparative study, thirty five patients with chronic plaque psoriasis were treated with either intradermal BoNT-A or 5-fluorouracil (5-FU). Treatment outcomes were assessed by two blinded observers and the criteria included induction scores, erythema, scaling and induration were evaluated. No significant difference was found between the two sides regarding the clinical response. The response rate was found to be 85% on the BoNT-A side and 90% on the 5-FU side [71].

10. Conclusion

In this chapter the current off-label use of BoNT-A in various clinical, non-cosmetic dermatological conditions, has been reviewed. The neuromodulator has a complex mechanism of action, which to date has not been fully elucidated. However, it is clear that there is great potential for its therapeutic use in various skin condition associated with pain, inflammation and with hyperhydrosis.

Many of these disorders are chronic conditions and consequently will require repeat injections of BoNT-A, hence it is important to establish the long-term safety and efficacy of the neuromodulator.

The long-term safety of BoNT-A is well-established, yet there remains the potential for tachyphylaxis with cyclical treatments since we know that BoNT-A has an immunogenic potential.

Experience with BoNT-A for cosmetic indications, where doses of up to 100 units are injected every 4–6 months, has shown a very low incidence of immunoresistance. Hence we may assume that the development of neutralising antibodies to BoNT-A is very rare. However, it appears that the key factors in this regard may be the treatment frequency and the dose injected per session.

The evidence to date for the clinical efficacy of BoNT-A in many of these conditions is based on Level V case reports, with diverse treatment protocols, and a very few randomised controlled trials.

Hence further systematic double-blind randomised trials with larger patient populations are warranted to establish the role of BoNT-A in these clinical non-cosmetic dermatological conditions. Furthermore, basic research into the role of BoNT-A in the modulation of neuropeptides and hence it effects on the cutaneous neuroimmune system are required. In conclusion, a consensus on the injection protocol and dosing regimen for each indication is essential.

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