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SHORT COMMUNICATION

Botulinum Toxin Type B for Hidradenitis Suppurativa: A Randomised, Double-Blind, Placebo-Controlled Pilot Study

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Abstract

Background Botulinum toxin (BTX) is a potent neurotoxin with a long history of therapeutic application in neurological and dermatological conditions, with a strong efficacy and safety profile.

Objective Our aim was to assess whether intradermal injection with BTX-B is an effective treatment for hidradenitis suppurativa (HS).

Methods Twenty patients with HS stage I–III disease, according to Hurley's classification, were consecutively included for treatment with either a placebo or BTX-B. At the next intervention after 3 months, all participants received the active substance and another follow-up at 6 months. The primary outcome was quality of life, measured using the Dermatology Life Quality Index (DLQI), while secondary outcomes were the visual analogue scale (VAS) for pain in the worst boil and HS-related impairment of general health (VAS), as well as changes in physician-reported disease activity assessed as the number of total lesions, and reported adverse effects of treatment.

Results The DLQI improved from a median of 17 at baseline to 8 at 3 months in the BTX-B group, compared with a reduction from 13.5 to 11 in the placebo group ($p < 0.05$). Improvement of the patients' own ratings of symptoms and a reduction in total lesions supplemented the primary outcome. Fifty-five percent of the study population reported some degree of hyperhidrosis.

Conclusion BTX-B improves the quality of life in patients with HS. Furthermore, comorbidity between HS and hyperhidrosis is suggested.

Trial Registration ClinicalTrials.gov identifier: NCT03103074.

Key Points

Injections with botulinum toxin type B improve the quality of life and self-assessed symptoms in patients with hidradenitis suppurativa.

Hyperhidrosis was a self-reported comorbidity in more than half of the hidradenitis suppurativa patients.

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1 Introduction

Hidradenitis suppurativa (HS) is a chronic skin disease characterised by painful, deep-seated, inflamed nodules, abscesses and, in the later stages, fistulas, sinus tracts and scarring in apocrine gland-bearing areas of the body [1, 2]. The understanding of the disease pathogenesis remains

incomplete and previously accepted models of HS pathogenesis are now being challenged. Occlusion of the hair follicle is paramount in the manifestations of HS, but the instigating mechanism of occlusion is controversial. Subsequent inflammation and combined innate and adaptive immune dysregulation lead to the development of skin lesions in HS [3].

HS has an estimated prevalence of 1–4% [4]. The average age of onset of HS is in the early 20s, and substantial data suggest a female predominance, with a 3:1 sex ratio [5, 6]. Additionally, HS is a condition associated with considerably impaired quality of life (QoL), depression and disability [7].

HS is difficult to treat and clinical practice is variable. The treatment of mild and moderate disease includes topical and systemic antibiotics, intralesional corticosteroids and retinoids, and limited surgical options [8, 9]. Tumour necrosis factor inhibitors are a treatment option for moderate to severe disease stages [10], while surgery is an important treatment option in the late stages with fistulas, sinus formations and scarring. Advice on lifestyle is crucial to prevent exacerbations of the disease.

Botulinum toxin (BTX) is a potent neurotoxin produced by the bacterium *Clostridium botulinum.* There are seven different isoforms (BTX-A, B, C, D, E, F and G), with BTX-A and BTX-B being commercially available. BTX blocks the release of acetylcholine and a number of other neurotransmitters from presynaptic vesicles, and has a long history of therapeutic application in neurological conditions, with a strong efficacy and safety profile. BTX is used in a number of dermatological conditions, such as hyperhidrosis, pruritic dermatoses and acantholytic disorders [11, 12]. BTX-B has a weak effect on α-motor neurons and muscles, with a ratio of 1:50–100 in favour of BTX-A. Conversely, BTX-B has an almost equipotent sudomotor effect compared with BTX-A [13]. This discrepancy in effect on muscles versus sweat glands makes BTX-B most suitable in the treatment of larger body surfaces without the threat of causing muscle weakness.

Five patients have previously received BTX-A injections for HS, with a positive outcome [14–17], whereas a study performed in five HS patients reported improvement in the Dermatology Life Quality Index (DLQI), but not for the number of nodules or VAS for pain [18].

The purpose of the current study was to evaluate the effect of BTX-B in a randomised, double-blind, placebo-controlled setting with respect to QoL, pain perception and number of lesions in HS.

2 Materials and Methods

2.1 Trial Overview and Population

This was a single-centre, randomised, double-blind trial performed in the outpatient clinic of the Department of Dermatology at the University Hospital of North Norway. The trial was conducted in accordance with the Declaration of Helsinki and monitored by Good Clinical Practice units. The Regional Committee for Medical and Health Research Ethics in North Norway granted ethical approval (2017/149/REK Nord) and all participants provided written informed consent prior to enrolment. This study was registered at ClinicalTrials.gov (NCT03103074).

Twenty patients with HS stage I–III disease, according to Hurley's classification, were consecutively included for injections with either a placebo (saline) or BTX-B (NeuroBloc®; Eisai, Sweden). Key exclusion criteria were emergency medical or surgical treatment of HS, pregnancy, breastfeeding and neuromuscular disease. Inclusion and exclusion criteria, as well as a Consolidated Standards of Reporting Trials (CONSORT) diagram, are provided in the Electronic Supplementary Material.

2.2 Interventions, Randomisation, Blinding and Study Drugs

The principal investigator responsible for the evaluation was blinded throughout the entire study, and participants were blinded until the first evaluation at 3 months; thereafter, all participants received a second injection procedure, unblinded, using BTX-B. A secondary investigator was responsible for the injections with interventional substances, after using the randomisation tool in the electronic data software tool (REDCap). At baseline, the study participants ($n=20$) randomised in a 1:1 ratio received either the active substance (BTX-B) or placebo. After 3 months, the blinded placebo-controlled setting was succeeded by an open setting in which the BTX-B group (B2) received a second treatment with BTX-B and the former placebo group (B1) was injected with BTX-B. As the two study groups (B2 and B1) received one and two BTX-B treatments, respectively, we calculated differences in each group separately with changes from baseline to the evaluation at 3 and 6 months post-treatment. One patient randomised to receive BTX at baseline dropped out before the 3-month visit due to a long travel distance to the study site.

BTX-B (NeuroBloc®) was diluted to 50 units (U)/mL in normal saline by the secondary investigator. Normal saline was used as a placebo. 0.05–0.1 mL of assigned solution was injected intradermally in a grid, with 1–1.5 cm between each injection in the affected areas and in the

perilesional healthy-appearing skin, with a maximum of 1300 U per injection session. The total dose per treatment area varied depending on the location of the disease, limited per field at up to 150 U/armpit, 200 U/groin, and 600 U in the perianal/perigenital areas. The maximum total dose allowed per treatment was 4000 U of BTX-B. Lesions in other locations, such as the inframammary area, periareolar area and abdominal fold were not assigned for intervention. Patients were offered topical anaesthesia with lidocaine/prilocaine cream (Emla®; Aspen Nordic, Denmark) under occlusion with plastic film 30 min prior to intervention.

Confounding HS treatments, such as antibiotics, local corticosteroid injections, adalimumab, isotretinoin and azelaic acid, were not allowed during the study.

2.3 Trial Outcomes

The primary objective of this study was to present QoL data in HS participants at baseline and 3 months after BTX-B injections, versus placebo, in a randomised, double-blind manner. The primary outcome was the DLQI [19]. Secondary objectives were to assess the pain from the worst boil, the participants' HS-related impairment of general health, the number of total lesions (nodules, abscesses and fistulas) and the adverse effects at baseline and at follow-up 3 months post-injection (BTX-B vs. placebo). Secondary outcomes were the rating of pain in the worst boil on a visual analogue scale (VAS), rating of the HS-related impairment of general health (VAS) on a VAS, counts of total lesions, and a report of possible adverse effects of treatment. The outcomes were aligned with the recently developed core outcome set for HS [20].

The Nordic Registry for HS (HISREG) was used for the registration of endpoints and baseline characteristics. In addition, all patients were investigated using the validated Hyperhidrosis Disease Severity Scale (HDSS) [21] at baseline to evaluate any existing comorbidity.

2.4 Statistical Methods

Descriptive statistics were used to compare the baseline characteristics of the trial participants. Continuous variables were summarised, as appropriate, using means with standard deviations or as medians with minimum and maximum values. Categorical variables were expressed as frequencies. Efficacy analyses compared treatment arms at month 3, using a rank analysis of covariance combined with Mantel–Haenszel statistics [22], with adjustment for the baseline value of the respective outcome variable. Within-group changes from baseline to 3 and 6 months were explored using graphical presentation and the Wilcoxon signed-rank test.

Table 1 Participant baseline characteristics

Characteristics	Placebo ($n=10$)	BTX-B ($n=10$)
Sex (n)		
Female	7	10
Male	3	0
Mean age (years)	37	38
Mean body mass index (kg/m^2)	34	33
Previous smoking status (n)	7	10
Current smoking status (n)	8	5
Mean age at onset of hidradenitis (years)	25	19
Mean age at first consultation with a dermatologist/specialist (years)	34	29
Affected skin area assigned for intervention (n)		
Axillae	2	3
Axillae + inguinal and crural fold	–	1
Inguinal and crural fold	4	4
Inguinal and crural fold + perianal/gluteal area	4	2
Hurley stage (n)		
I	8	6
II	2	3
III	0	1
Hyperhidrosis severity score [HDSS] (n)		
HDSS grade 2	4	4
HDSS grade 3	1	2

BTX-B botulinum toxin B, *HDSS* Hyperhidrosis Disease Severity Scale

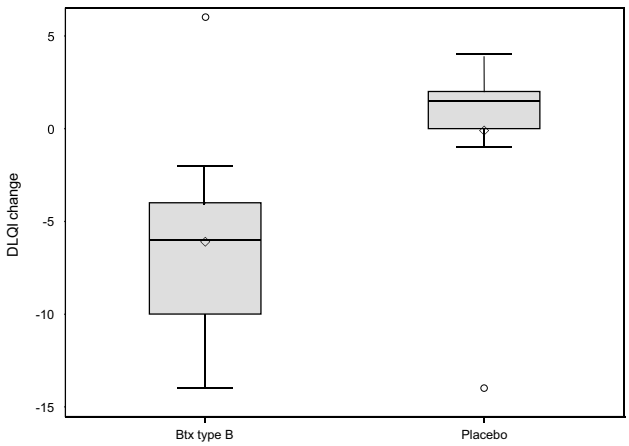

Fig. 1 The primary outcome, DLQI, improved from baseline to follow-up at 3 months in the BTX-B group ($n=10$) compared with placebo ($n=10$, $p<0.05$). Change in DLQI with medians (straight line), means (open diamond), outliers (open circle) and spread are shown in the figure. *DLQI* Dermatology Life Quality Index, *BTX-B* botulinum toxin B

For all tests, the level of significance was set at $p<0.05$. Due to the exploratory nature of this study, no adjustments for multiple comparisons were undertaken, and p values

should not be used to infer definitive treatment effects for secondary outcomes. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3 Results

The study population had an expected predominance of female participants (17 of 20), current smokers (13 of 20) and a high median body mass index (BMI; 32 kg/m^2) Three (15%) patients in the study population experienced severe hyperhidrosis (HDSS 3), and eight (40%) patients experienced mild to moderate hyperhidrosis (HDSS 2) (Table 1).

The primary outcome, DLQI at 3 months, improved from a median of 17 (maximum 21; minimum 10) to 8 (maximum 22; minimum 0) in the BTX-B group, compared with an improvement from a median of 13.5 (maximum 21; minimum 2) to 11 (maximum 20; minimum 1) in the placebo group (p <0.05) (Fig. 1). The patients' own rating of HS-related impairment of general health on the VAS (1–10) improved in the BTX-B group, from a baseline median of 8 (maximum 10; minimum 6) to post-treatment of 3.5 (maximum 9; minimum 0), compared with a median of 6.0 (maximum 10; minimum 2) to 5.5 (maximum 10; minimum 1) in the placebo group (p <0.05) (Table 2). In addition, the number of total lesions and the

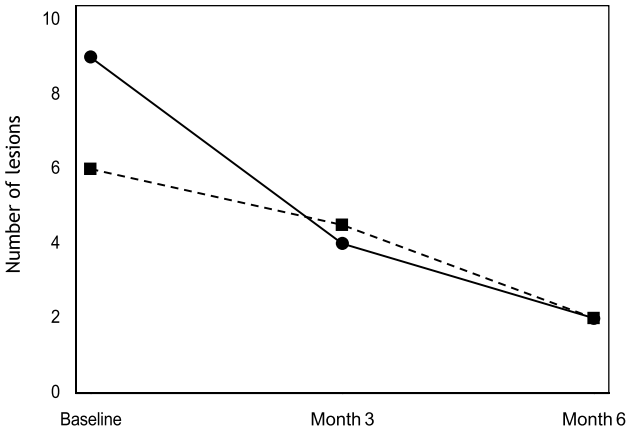

Fig. 2 Total number of lesions (nodules, abscesses, fistulas) decreased from baseline in the BTX-B group (filled circle) after first (p <0.01) and second (p <0.01) BTX-B injections. In the placebo group (filled square), a slight decrease of lesions was seen at 3 months (not statistically significant), but, in an open setting, a clear decrease from baseline was seen at 6 months when BTX-B was administered (p <0.05). *BTX-B* botulinum toxin B

Table 2 Results from patients in group B1 (who received one placebo and one BTX-B treatment) and B2 (who received 2 BTX-B treatments)

	B1 group (placebo × 1, BTX-B × 1)				B2 group (BTX-B × 2)			
	Median	Mean	SD	*p* value	Median	Mean	SD	*p* value
DLQI								
Baseline	13.5	10.7	7.2		17	16	4.4	
3 months	11	10.6	7	NS	8	9.9	6.8	*< 0.05*
6 months	6.5	6.1	4.4	0.07	14	11	6.9	*< 0.01*
HS-related impairment of general health (VAS)								
Baseline	6	5.8	2.7		8	7.7	1.4	
3 months	5.5	5.6	3.1	NS	3.5	3.8	2.5	*< 0.01*
6 months	4.5	4	2.5	0.11	7	5.1	3.2	*< 0.05*
Number of nodules								
Baseline	6	5.9	2.6		7.5	7.3	2.3	
3 months	2	5.8	9.1	NS	3.5	3.4	2.6	*< 0.01*
6 months	1	2.8	5.1	0.06	2	2.4	2.1	*< 0.01*
Total number of lesions								
Baseline	6	8.3	5.5		9	8.5	2.6	
3 months	4.5	7.7	9.6	NS	4	4.6	4	*< 0.01*
6 months	2	3.8	5.6	*< 0.05*	2	2.9	2.9	*< 0.01*
Pain in the worst boil (VAS)								
Baseline	7	6.6	2.3		8	8.3	1.1	
3 months	7	7	1.3	NS	6	6	2.8	0.09
6 months	6.5	6.1	2	NS	5	4.8	3.3	*< 0.05*

n = 10 in each group at baseline. At 3 months and 6 months, n = 10 and 9 respectively for B1 and B2

BTX-B botulinum toxin B, *DLQI* Dermatology Life Quality Index, *HS* hidradenitis suppurativa, *NS* non-statistically significant, *SD* standard deviation, *VAS* Visual Analogue Scale (1–10)

experiences of pain (measured on the VAS) were reduced in the BTX-B group, but the differences between groups were non-significant. A significant reduction in total lesions from baseline was seen in the B2 group at both 3 and 6 months ($p < 0.01$). In the B1 group, no significant difference was obtained at follow-up in 3 months (after placebo), but the number of total lesions improved after BTX-B injections at follow-up in 6 months ($p < 0.05$) (see Fig. 2).

Besides the changes in total lesions, improvement from baseline was also seen in the B2 group after 3 months in terms of DLQI ($p < 0.05$), HS-related impairment of general health (VAS) [$p < 0.01$] and number of nodules ($p < 0.01$), and at 6 months in terms of DLQI ($p < 0.01$), VAS for pain in the worst boil ($p < 0.05$), number of nodules ($p < 0.01$) and HS-related impairment of general health (VAS) [$p < 0.05$].

As expected, no significant changes were seen regarding outcomes after placebo in the B1 group at the 3-month evaluation. Besides the reduction in total lesions ($p < 0.05$), a tendency for improvement in the DLQI, from a median of 13.5 at baseline to 6.5 ($p = 0.07$), VAS HS-related impairment of general health ($p = 0.11$), and number of nodules ($p = 0.06$), was seen at the 6-month follow-up.

No adverse effects were reported. One patient in the placebo group required surgery of a draining sinus during the intervention period.

4 Discussion

This randomised, double-blind, placebo-controlled study clearly showed that BTX-B improves QoL and self-assessed symptoms in HS. Additionally, total lesions were reduced in the active group at 3 and 6 months, respectively, as well as after BTX-B in an open setting in the former placebo group. Our pilot study confirms previous case reports [14–17] with a positive outcome of BTX treatment in HS and encourages further interventional studies.

A main goal in the treatment of HS is to prevent the development of nodules into abscesses, fistulas and sinus formations. At baseline in this study, inflammatory nodules were predominant, with all participants having Hurley stage I–II, except for one participant who had Hurley stage III. After BTX-B, nodules reduced over time, with less pain and improved QoL. As a consequence of the results of this study, we are gradually changing our treatment routines for HS in our dermatological clinics. We frequently treat involved areas with BTX-B, combined with local nodular corticosteroid injections and advice on lifestyle. In addition to the effect on pain and the impact on life, we hope this can prevent scarring and the formation of fistulas and sinuses in patients with Hurley stage I–II HS.

The mechanistic explanation of the amelioration of HS with BTX treatment is speculative. The microbiota differs between regions of oily and moist skin [23, 24]. Tentatively, the anhidrotic effect of BTX-B in intertriginous areas may have an impact on the microbiome and bacterial growth, and subsequently inhibit an important factor in the pathogenesis. To further confirm a change in bacterial flora from BTX-B, another study examining both the quantitative bacterial flora and the qualitative number of different bacteria would be necessary.

HS is a follicular acneiform disease in the area in which apocrine sweat glands are located. The role of the apocrine sweat gland in HS is not fully understood. In HS, antimicrobial peptides (AMPs) are excessively secreted, in particular by the apocrine sweat glands, distal hair follicle epithelium and epidermis [25]. AMPs trigger inflammation and thus facilitate or promote HS development. The apocrine gland responds to adrenergic substances, but whether or not cholinergic substances have an effect on apocrine sweat secretion is more obscure [26, 27]. BTX-A, which inhibits cholinergic innervation, has an effect on bromhidrosis, and histological studies show apocrine sweat glands with atrophic changes and hypoplasia in skin treated with BTX-A [28–30]. One might speculate as to whether BTX-B has an effect on HS through decreasing the production of apocrine sweat. In a recent publication, BTX-A treatment of five HS patients and concomitant excessive sweating did not demonstrate a notable improvement in HS scoring or on patient-reported assessment of pain. However, an impact on the QoL of patients with lesions of concurrent HS and hyperhidrosis activity was observed in a majority of the patients. The authors interestingly attribute the improvement, in part, to the positive effect on hyperhidrosis [18].

In general, neurogenic inflammation precedes and augments immunological inflammation. BTX inhibits neurogenic inflammation by attenuation of neurotransmitter release (glutamate, substance P and calcitonin gene-related peptide) and reduction of inflammatory cell infiltration [31–34]. Furthermore, the nociceptive innervation of mast cells is also inhibited by BTX-B [35]. Mast cells are present, to a greater degree, in HS lesions than in perilesional skin, and, in a recent paper, disease severity has been shown to correlate with the number of mast cells and with itch [36]. Therefore, the inhibitory effect of BTX on neurogenic inflammation and nociceptive mast cell innervation is a plausible explanation of the results of this study.

BTX-A inhibits exocytosis in cholinergic post-ganglionic nerve-end terminals to sweat glands, as well as muscles. BTX-B has an almost equally anhidrotic effect as BTX-A [13] but only 1–2% of the antimuscular effect of equipotent (1:1) doses of BTX-A [37]. This means that large areas can be treated with BTX-B without muscular adverse effects, and up to 4000 U of BTX-B is considered to be well-tolerated in

regard to adverse effects and immunisation. This characteristic of BTX-B is of great value when injecting in HS, where there are many affected intertriginous areas. In this study, no adverse effects from BTX-B were reported. Pregnancy, breastfeeding and neuromuscular diseases are still contraindications in the use of BTX-B.

Smoking is a well-known aggravating factor in HS. Nicotine may induce an infundibular epithelial hyperplasia, and thus follicular plugging, in HS patients [38]. Furthermore, nicotine induces sweating by the sudomotor axon reflex [39], which may lead to hyperhidrosis [40] with a favourable environment for bacterial growth. In addition to smoking, obesity is strongly associated with HS. Mechanical stress factors or trauma play a role in obese patients with HS [41]. Obesity facilitates skin friction, increases intertriginous sweating, induces the production of proliferative factors such as insulin-like growth factor-1 and promotes an androgen profile in women. As expected, smoking and obesity were common in the current study population, making advice on lifestyle important.

Inflammatory bowel disease, ankylosing spondylitis, acne conglobata, pyoderma gangrenosum and metabolic syndrome are well-known conditions associated with HS [42]. Surprisingly, 15% of the study population experienced severe hyperhidrosis (HDSS grade 3) and a further 40% experienced mild to moderate hyperhidrosis (HDSS grade 2). The prevalence of hyperhidrosis is estimated to be about 3% of the general population [43]. In a large cross-sectional study of adolescents in Israel, a gradual increase was seen in the prevalence of hyperhidrosis, from underweight to obese, in both male (1.5–2.9%) and female (1.1–1.6%) participants [44]. The current study supports the association between hyperhidrosis and HS [18]. If increased eccrine sweating occurs in HS individuals in general, the idea of using BTX-B is even more logical.

A potential weakness of this study is the small sample size. In addition, several patients included in this study had HS activity in locations that did not receive treatment with the investigational drug. Therefore, the reported improvement in DLQI and VAS may have been underestimated as these scores do not report site-specific activity in the treated area. The high percentage of patients with hyperhidrosis in this study may have caused confounding of the primary endpoint, the DLQI, since hyperhidrosis is known to affect QoL to a large degree.

5 Conclusion

In our study, treatment with BTX-B improved the QoL in patients with HS, which could be explained by a reduction in total lesions. Hyperhidrosis has not been previously reported as a comorbidity of HS in clinical studies, but our findings indicate that HS and hyperhidrosis co-exist.

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Author Contributions Conceptualisation, formal analysis and investigation, writing (review and editing): ØG, BØK and CS; Methodology, writing (original draft preparation): ØG and CS.

Declarations

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Conflict of interest Carl Swartling is a shareholder in Hidros International and is the owner of sweat clinics in Stockholm and Oslo. Øystein Grimstad and Bjørn Øivind Kvammen report no conflicts of interest.

Ethics Approval This study was conducted in accordance with the ethical standards of the responsible committees and the Declaration of Helsinki, and with the International Conference on Harmonization Guidelines for Good Clinical Practice. The trial was overseen by an independent Data and Safety Monitoring Board.

Institutional Review Board Approval Status The Regional Committee for Medical and Health Research Ethics in North Norway granted ethical approval (2017/149/REK Nord).

Consent to Participate Written informed consent was obtained from all patients or their proxies.

Consent for Publication Not applicable.

Data Availability Statement The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Code Availability Not applicable.

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