Intralesional Botulinum Toxin A Injection for Recalcitrant Alopecial Totalis and Alopecia Universalis: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Background: Alopecia totalis (AT) and alopecia universalis (AU) have a high rate of recurrence and are very difficult to treat. To date, no consensus has been reach among clinicians regarding the best way to treat these conditions. It was recently proposed that botulinum toxin type A (BT) injection in alopecia areata may inhibit unmyelinated C fibers from releasing substance P and calcitonin-gene-related protein (CGRP), which showed a favorable clinical response in cephalalgic alopecia areata.

Objective: To investigate the efficacy of botulinum toxin type A (BT) in the treatment of recalcitrant AT and AU.

Methods: Twenty patients with either recalcitrant AT or AU were enrolled in this study. One half of the scalp was injected with BT 50 units 2.5 ml intradermally (dilution 20 units/ml) and the other half of the scalp was injected with normal saline 2.5 ml. Clinical assessments were performed using Severity of Alopecia Tool (SALT) score, scalp mapping, and photography. Patients were followed up monthly for 4 months after treatment to evaluate terminal hair regrowth.

Results: Based on patient results at the 4-month follow-up, no clinical improvement in either recalcitrant alopecia totalis or alopecia universalis was observed.

Conclusion: Although BT has been demonstrated to improve the clinical features of cephalalgia alopecia areata, BT was not shown to improve the clinical features of recalcitrant AT or AU in this study. In order to understand and explain the differences in these two clinical outcomes using BT in alopecia, further investigation is needed.

Keywords: Intralesional botulinum toxin A injection; alopecial totalis; alopecia universalis; recalcitrant alopecial totalis; recalcitrant alopecial universalis (Siriraj Med J 2017;69:1-4)

INTRODUCTION

Alopecia areata (AA) is a common cause of non-scarring hair loss. The clinical manifestations of AA include a variety of potential hair loss outcomes. AA typically begins with small areas of patchy hair loss, then may spontaneously reverse completely, become chronic, or may progress to complete scalp hair loss (alopecia totalis, AT) or entirely body hair loss (alopecia universalis, AU).[5]

There are many treatments for AA, with treatment depending on the age of the patient and the extent of the lesions. Treatments include topical corticosteroids, minoxidil solution, intralesional steroids, oral corticosteroids, intramuscular corticosteroids, topical immunotherapy, and immunosuppressive agents.[2,6,7,8] Previous studies have reported success using intramuscular injection of botulinum toxin type A (BT) in the treatment of cephalalgia alopecia areata (alopecia areata with headache).[1,3] The objective of this study was to investigate the efficacy of BT in the treatment of recalcitrant AT and AU.

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MATERIALS AND METHODS

Study design

This randomized, double-blind, placebo-controlled trial employed a split-scalp design to evaluate the efficacy of BT in the treatment of AT and AU. In each of our 20 study participants, one side of the scalp was injected with BT 50 units (Concentrated botulinum toxin type A (BT) (Botox®; Allergan plc, Dublin, Ireland) which was diluted to a concentration of 20 units per milliliter) and the other side of the scalp was injected with normal saline solution (NSS).

Given that no previous study has been undertaken to investigate BT as a treatment for AT and/or AU, there was no precedent to which to refer regarding sample size. As such, a total of 20 participants were enrolled, including patients diagnosed as either AT or AU.

Patients

Twenty patients with recalcitrant AT or AU from the Hair Clinic of the Department of Dermatology, Faculty of Medicine Siriraj Hospital were recruited. Patients eligible for enrollment in this study must have been: (1) at least 18 years of age; and, (2) patients who did not respond to all prescribed treatment modalities at the Siriraj Hair Clinic, to include topical and systemic corticosteroids, topical minoxidil, oral ciclosporin, and DCP (diphenylcyclopropenone) for more than 24 months. Exclusion criteria included scalp infection or inflammation; history of allergy to botulinum toxin or human albumin; pregnancy or lactation; and, patients with neurologic conditions, such as myasthenia gravis or Lambert-Eaton syndrome. The protocol for this study was approved by the Siriraj Institutional Review Board [Si.615/2552 (EC2)] and written informed consent was obtained from all study participants.

Evaluation

According to the alopecia areata investigation guideline, the SALT (Severity of Alopecia Tool) score was determined by a blinded physician to assess the efficacy of treatment at baseline and at the week 1, 1 month, 2 months, 3 months, and 4 months follow-up visits. Photographs were also taken at baseline and at each follow-up visit. To ensure consistency, standardized views at defined distances between patient and camera were taken in the same studio. Patient history was taken and clinical examinations were performed to assess any adverse effects of treatment.

Statistical analysis

Data were analyzed using SPSS Statistics version 18 (SPSS, Inc., Chicago, IL, USA). Demographic data were presented using descriptive statistics and continuous data were reported using mean±SD. Independent samples t-test was used to compare between BT and NSS treatments. Pretreatment and posttreatment comparisons were evaluated using repeated measures ANOVA (RM-ANOVA). A *p*-value of less than 0.05 was considered statistically significant.

RESULTS

All subjects (10 females and 10 males) completed the treatment and attended all follow-up visits. Two of twenty participants (10%) were diagnosed as alopecia totalis and the remaining 18 were alopecia universalis. Age of patients ranged from 19 to 73 years (mean±SD, 31.2±11.2). Age of onset of alopecia ranged from 12 to 72 years (mean±SD, 25.5±12.6) and duration of alopecia ranged from 1 to 13 years (mean±SD, 5.7±3.4). Forty-five percent (9/20) of patients had nail abnormalities, with nail pitting observed in the majority of those 9 patients. Demographic and clinical data of study participants are shown in Table 1.

A comparison of baseline SALT scores between the BT-treated scalps and the NSS-treated scalps was not different (p=0.92). At the 1 month follow-up, the mean SALT score for the BT-treated scalps and the NSS-treated scalps was 46.27% and 45.97%, respectively. SALT scores were not significantly different between groups ($p \geq 0.05$). Similar to the SALT score findings at the 1 month follow-up, there were no significant differences in SALT score between groups at any of the subsequent monthly follow-up visits (Table 2).

DISCUSSION

Hair follicles (HFs) are characterized by downregulation of major histocompatibility complex (MHC) class I and local expression of potent immunosuppressants results in relatively immune privilege (IP). [4] A disruption in or discontinuation of IP may lead to alopecia areata (AA), but the pathophysiology is still not clearly understood and AA is still assumed to be a multifactorial disease.[6] Strong evidence involving T cell activation suggests an autoimmune etiology, although an autoantigen has not yet been identified. Other causes have also recently been studied, including genetic and environmental factors. Environmental factors, such as infection or stress may mediate the release of some neuropeptides from follicular nerve endings. Other evidence, including increases in substance P[5] and decreases in calcitonin-gene-related protein (CGRP), was found in hair follicles affected by alopecia.

TABLE 1. Demographic and clinical data of study participants.

Case no.	Gender	Age (yr)	Age of onset (yr)	Duration of alopecia (yr)	Diagnosis	Underlying disease	Family history of AA	Nail abnormality	Baseline SALT score
1	Male	31	18	12	AU	None	Unknown	None	100
2	Female	27	22	5	AT	None	None	None	54
3	Female	32	28	4	AU	None	Yes	None	48.8
4	Male	35	32	3	AU	None	Unknown	None	100
5	Male	19	14	5	AU	Allergic rhinitis	Unknown	None	64.4
6	Female	34	28	6	AU	Allergic rhinitis, hyperthyroidism, thyroid cyst	Unknown	Pitting nail	100
7	Male	31	28	3	AU	None	Unknown	None	100
8	Male	37	25	13	AU	None	Unknown	Pitting nail	90
9	Female	27	20	7	AU	None	Unknown	None	100
10	Female	31	27	4	AU	None	Unknown	None	100
11	Male	26	18	8	AU	Asthma	Unknown	None	100
12	Male	33	28	5	AU	Allergic rhinitis	Unknown	Pitting nail	100
13	Female	24	12	12	AU	None	Unknown	Pitting nail	100
14	Female	39	35	4	AU	Hypothyroidism	Unknown	Pitting nail	100
15	Male	20	17	3	AU	None	Unknown	None	100
16	Male	33	28	5	AU	None	Unknown	Pitting nail	100
17	Male	23	15	8	AU	None	Unknown	Pitting nail	100
18	Female	73	72	1	AT	Dyslipidemia, hypertension	Unknown	Nail onychorrhexis	100
19	Female	28	27	1	AU	None	Unknown	Twenty-nail dystrophy	100
20	Female	21	15	6	AU	None	Unknown	None	100

TABLE 2. SALT score relative to BT and NSS findings at follow-up months 1 through 4 [mean (SD)].

SALT score	Botulinum toxin [mean (SD)]	NSS [mean (SD)]	*p*-value
Baseline	46.56 (7.82)	46.3 (8.55)	0.92
1 mo. F/U	46.27 (8.29)	45.97 (8.86)	0.91
2 mo. F/U	46.3 (8.23)	45.84 (9.18)	0.87
3 mo. F/U	47.43 (5.86)	47 (6.77)	0.83
4 mo. F/U	47.12 (6.31)	46.96 (6.90)	0.94

Abbreviations: SALT = Severity of Alopecia Tool; NSS = normal saline solution; F/U = follow-up *p*-value <0.05 indicates statistical significance

Alopecia totalis (AT) and alopecia universalis (AU) both have high rates of recurrence and are very difficult to treat. Hair loss and other clinical features associated with AT and AU also contribute to high adverse impact on patient quality of life. Until now, standard first-line treatment remains the weekly application of DCP[2], although new treatment methods are being developed and evaluated. Application of DCP is time-consuming and requires very good patient compliance. In addition, the clinical response rate from DCP treatment in AT/AU has been shown to be less than 70%.[2]

A recent study postulated that BT injection in alopecia areata may inhibit unmyelinated C fibers from releasing substance P and calcitonin-gene-related protein (CGRP), which can stop the destruction of hair follicles and shows a favorable clinical response in cephalalgic alopecia areata.[1,3] It was, therefore, possible that BT injection might be a new treatment modality for cases of AT and AU which don't respond to DCP. Accordingly, this study was conducted to evaluate the efficacy of BT injection in the treatment of recalcitrant AT and AU.

At the conclusion of the study, none of the 20 patients showed any clinical improvement from BT injection treatment. Moreover, there were no statistically significant differences in SALT score between groups at each of all follow-up visits. This data suggests that AT and AU may have a different pathophysiology from caphalalgic alopecia areata that showed improvement from intramuscular BT injection. AT and AU may not involve substance P and CGRP, so BT may not be able to reverse the pathology of this disease. Another explanation involves the dosage of BT, which may not have been enough to effectively treat recalcitrant AT and AU. The dosage that we used in this study (BT 50 units in one side) was derived from a study of cephalalgia alopecia areata by Cutrer, in which they treated the headache with botulinum A toxin injected into procerus, corrugator, frontalis, temporalis, splenius capitus, occipitalis and trapezius muscles (100 units total). Hsu, et al, found that 0.1 ml of this BT at concentration 20 units per milliliter could effectively cover 6.05 cm^2 of scalp area, so BT 50 units can cover around 150 cm^2. From calculation we estimated that the scalp area varied from 250-400 cm^2, so BT 50 units may not cover the half of the scalp or that dosage may be different than the dosage that is needed to suppress lymphocytic infiltration. The last possible explanation involves the transitional nature of alopecia areata. AA is initially a non-scarring alopecia that evolves into a scarring alopecia over time. We recruited only recalcitrant cases of AT and AU, so the possibility of irreversible scarring must be considered.

The existing clinical evidence supports the potential clinical value of BT in the treatment of patients that suffer from disorders that fall within the AA group of diseases. However, further studies are needed to elucidate suitable doses of BT and routes of administration relative to each AA-related disorder.

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Conflict of interest declaration

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

Funding disclosure

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