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BRIEF REPORT

Real-World, Retrospective, Multicenter, Observational Study on the Use of the First Liquid AbobotulinumtoxinA in Italy

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ABSTRACT

Introduction: Randomized controlled trials (RCTs) suggested that liquid formulation of botulinum toxin type A (aboBoNT-A) is safe and effective, but data confirming these characteristics in a real-life heterogenous set of patients are currently lacking. This study aimed to assess the efficacy and safety of the ready-to-use aboBoNT-A solution in adults with moderate-to-severe glabellar wrinkles.

Methods: In this real-life, multicenter, retrospective, observational study, healthy adults were treated at baseline only with aboBoNT-A solution on the glabellar area and followed up for 24 weeks. Re-treatment after 20–24 weeks could also be combined with other aesthetic procedures. Family history of immune-mediated inflammatory diseases (IMIDs) was not an exclusion criterion.Patient-reported outcomes (patient's satisfaction and injection-related pain) and physician-reported outcomes (Physician Global Assessment, PGA) were collected.

Results: Of the 542 patients enrolled in the study, 38 had IMID family history. Injection-related pain was reported in 128 (23.62%) as mild (pain VAS = 1.34 ± 0.87) mainly by non-botulinum toxin treatment-naïve women under 50 years of age. At 48 h, physicians rated the clinical result as "improved" in 64% of patients,

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conversely 264 patients (48.71%) self-evaluated as "satisfied"/"very satisfied". At 4 weeks a touch-up (< 10 units) was performed in 11 (2.03%) patients and 98.2% were "highly satisfied". Re-treatment was performed in 330 (61.45%) patients, mainly botulinum-experienced, at 20 weeks and in 207 (38.55%), mainly botulinum naïve, at 24 weeks. A total of 403 (74.35%) patients were re-treated with the three-point technique and 201 (37.08%) also received hyaluronic acid filler in the lower central face and middle third. There were no cases of de novo IMIDs.

Conclusions: Real-world data confirmed that aboBoNT-A is a fast, efficient, durable, reproducible, and easy-to-use drug which is also well tolerated in patients with family history of IMID.

Keywords: Botulinum toxin type A; Liquid toxin; Glabellar wrinkles; Efficacy; Safety; Immune-mediated inflammatory diseases (IMIDs); Real-life; Telemedicine

Key Summary Points
Botulinum toxin use displays a well-established efficacy and safety profile.
Experts claim a moderate intra-observer, and even inter-observer, variability of the clinical results due to several factors (i.e., reconstitution).
The study aimed to assess the efficacy and safety of the ready-to-use aboBoNT-A solution in moderate-to-severe glabellar wrinkles.
The liquid toxin is an efficient, durable, reproducible, easy-to-use drug that allows clinicians more time availability (owing to no reconstitution time).

INTRODUCTION

The use of botulinum toxin in dermatology, plastic surgery, and aesthetic medicine has increased rapidly over the years, and it is the most common cosmetic procedure performed worldwide [1, 2]. Interestingly, the introduction in the 1990s of a beauty model based on a youthful appearance and the absence of wrinkles on the face has facilitated the rapid growth of botulinum toxin injections in both men and women [1].

Despite the escalating popularity of this aesthetic procedure supported by its well-established efficacy and safety profile [2], experts claim a moderate intra-observer, and even inter-observer, variability of the results that could be ascribed to several factors including (a) inter-individual anatomical differences, (b) inconstant technique reproducibility, (c) different formulations, (d) errors in reconstitution of lyophilized preparations, (e) injector sensitivity, and (f) dosage per point.

Several consensuses highlighted the need for a ready-to-use liquid formulation of BoNT-A (botulinum toxin type A) as well as a precise, easy-to-use, and dedicated injection device to facilitate and standardize injection practice [3]. In 2021 the first ready-to-use formulation, aboBoNT-A solution for injection, received the marketing authorization in several European countries, including Italy. It offers potential benefits over existing powder formulations, in convenience, consistency, and precision of dosing, because there is no need for reconstitution. Moreover, the formulation contains no human- or animal-derived excipients. Published placebo-controlled data from phase II and III studies have demonstrated that a 50-U dose of aboBoNT-A solution is efficacious and well tolerated when used to treat moderate-to-severe glabellar lines after single and repeated treatments, with high subject satisfaction [4, 5]

Although results from these clinical trials are encouraging, up to now, no real-life data on the heterogenous Italian population were available in literature that may support physicians' practice.

The aim of the present study was to assess the efficacy and safety of the ready-to-use aboBoNT-A solution in adults with moderate-to-severe glabellar wrinkles, treated with the new drug in a real-life setting.

MATERIALS AND METHODS

Ethics

The study protocol fulfilled the principles of Helsinki declaration of 1975 (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/), revised in 2013. The present study received the approval by the Institutional Review Board of San Raphael Hospital (protocol code 178/INT/2021, date of approval 10 November 2021, post hoc analysis). All subjects were informed and signed a consent form before enrollment.

Study design

This real-world, retrospective, observational, 24-week study involved patients admitted to IRCCS Galeazzi Hospital for the annual nevi screening who had received Alluzience® in one of nine Italian private clinics spanning the whole Italian mainland (Northern, Central, and Southern areas), namely Palermo ($N = 1$), Milan ($N = 2$), Bologna ($N = 1$), Venice ($N = 1$), Florence ($N = 1$), Bari ($N = 1$), Genova ($N = 1$), and Vigevano ($N = 1$). The study started in January 2022 and ended in September 2022, with an enrollment period of 2 months (January and February).

All physicians that performed the treatment had to be experienced (> 5 years) and board certified in dermatology or in plastic surgery.

Overall, the study protocol was based on five time points:

(a) At baseline (T_0), patients underwent a clinical visit including medical history, physician evaluation, and facial pictures at rest and at maximum frown. Treatment of glabellar lines with aboBoNT-A solution was carried out by administering 10 units into each of the five sites, as per product label.
(b) After 48 h post treatment (T_1), a consultation was carried out and pictures were taken.
(c) After 4 weeks post treatment (T_2), a clinical assessment plus picture was performed for possible touch-up.
(d) After 20 weeks from baseline (T_3), a clinical evaluation and a picture were scheduled to evaluate a potential re-treatment.
(e) After 24 weeks from baseline (T_4), a clinical assessment plus picture and a possible treatment were performed in patients who had not undergone re-treatment at T_3.

Re-treatment after 20–24 weeks could also be combined with other aesthetic procedures.

Inclusion/Exclusion Criteria

Treatment eligibility criteria were adult healthy patients (> 18 years) with or without atopic diathesis [6] that apply sunscreen Sun Protection Factor (SPF) 50+ and UVA-PF 5 daily on sun-exposed areas and who agreed to sign a consent form. Patients enrolled used botulinum toxin only for aesthetic purposes.

Conversely, patients were excluded in case of (a) acute or untreated chronic inflammatory/autoimmune diseases (e.g., psoriasis), (b) multiple chemical sensitivity [7], (c) addictions (excluded smoking) and body dysmorphic disorder, (d) acute or chronic infectious diseases (i.e., hepatitis B), (e) vaccines inoculated in the previous 3 weeks, (f) active facial mask- or non-mask-induced dermatosis, or (g) treatment with botulinum toxin in the glabellar area in the previous 16 weeks.

Clinical Evaluation

During the visit, demographics, Fitzpatrick's skin phototype, and medical history were collected; then a clinical evaluation was performed and, when needed, a dermatoscopy evaluation (dermatoscope with at least ×20 magnification and polarized light) was carried out to exclude dermatoses or atypical lesions in the facial area

to be treated. Clinical and demographic data were carefully collected. During the visit physicians administered the Body Dysmorphic Disorder Questionnaire (BDDQ) [8]. Facial pictures were collected in frontal projection with 300 DPI resolution and glabellar wrinkles were evaluated with the Four-Point Clinical Severity Score for glabellar frown lines at T_0 and T_2 [9].

Pain during injection was rated by patients with a pain visual analog scale (VAS) ranging from 0 (absence) to 10 (most intense pain ever experienced).

Patient's satisfaction was rated with a five-point categorical scale from 0 (very satisfied) to 4 points (very dissatisfied) [5]. The overall treatment response was assessed by physicians using the Physician Global Assessment (PGA), based on a nine-point descriptive scale, from − 4 (markedly worse) to + 4 (markedly improved).

Aesthetic Treatment

AboBoNT-A solution (Alluzience, Ipsen Ltd, Slough, UK/Galderma SA, Lausanne, Switzerland) was administered at the recommended dose of 0.25 ml of solution (50 units) divided equally across five injection sites, i.e., 0.05 ml of solution (10 units) administered intramuscularly into each site: two injections into each corrugator muscle and one into the procerus muscle, in line with the approved summary of product characteristics. All injections were performed with a marketed syringe that allows controlled release of the exact dose to administer (3Dose^{TM} 1 ml Syringe 125 Green, Vlow Medical B.V., Eindhoven, the Netherlands).

No concomitant treatment (i.e., fillers) was allowed in the same session, even in other facial areas at T_0; conversely at T_3 or T_4, physicians could decide to perform synergically other aesthetic treatments or even modify the toxin injection technique.

The treatment was repeated at T_3 or T_4 if subjective satisfaction had returned to baseline level or the patient had asked for a re-treatment.

Statistics

Data were computed as means ± standard deviations for continuous variables, whereas they were expressed as percentages in the case of categorical parameters. Student's *t* test for paired samples was applied to compute the mean differences between the five-point categorical scale at different time points.

All statistical analyses were carried out with the commercial software MedCalc Statistical Software version 17.9.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2017). Each *p* value less than 0.05 was considered statistically significant.

RESULTS

Patients' Demographics and Clinical Characteristics

A total of 542 patients (465 women, 73 men, 1 transgender, and 3 non-binaries) were enrolled. The average age of participants was 48.7 ± 17.5 years and the average body mass index (BMI) was 27.5 ± 2.4 kg/m^2. On evaluation of skin, 471 (86.90%) patients had a type III phototype and 71 (13.10%) had a type IV phototype.

Education level was also evaluated, and 2 patients (0.37%) completed middle school, 37 completed (6.83%) high school, 294 (54.24%) had a bachelor's degree, 197 (36.35%) had a master's degree, and 12 (2.21%) had a doctorate or postdoctoral degree.

The sample included 79 smokers, namely 31 only smoking conventional cigarettes, 7 only vaping, 22 only using e-cigarettes, and 19 using both cigarettes and vaping/e-cigarettes. In our cohort 297 patients had received previous botulinum toxin treatments while 245 were botulinum toxin naïve.

Outcome From Follow-up Visits

At T_0, 128 (23.62%) patients reported pain at the injection site during the treatment (pain VAS = 1.34 ± 0.87 in the whole sample) with a

prevalence in younger (under 50 years of age) non-botulinum toxin treatment-naïve women. At baseline 39 (7.20%) patients presented with type I severity of glabellar lines, 317 (58.49%) with type II, and 186 (34.32%) with type III.

Three patients met the criteria for needle phobia/trypanophobia (fear of injections, ICD-10 code F40.231).

At T_1, after 48 h post treatment, the percentage of satisfied/very satisfied patients according to the five-point categorical scale was 48.71% (264 patients) compared to 0% at baseline. The PGA score was assigned by physicians in 64.00% of the cases as "improved". Sixty-one patients reported transitory redness and three patients reported the onset of a wheal at the injection site.

At T_2 only 11 (2.03%) patients received a touch-up to refine the aesthetic result with a total dose that never exceeded 10 units. Overall, patients' satisfaction was high (98.2% highly satisfied) with a statistically significant improvement ($p < 0.001$) of the Four-Point Clinical Severity Score for glabellar frown lines. Specifically, 78 (14.39%) patients achieved type 0 severity of glabellar lines, 347 (64.02%) type I, and 117 (21.59) type II (Fig. 1). No correlation was found between patient's satisfaction rate and gender or scholarity.

Remarkably, no cases of asymmetry or short-term side effects (e.g., headache) were detected.

A re-treatment was performed in 330 (61.45%) patients at T_3 and in 207 (38.55%) at T_4. Five patients were recorded as treatment dropout. Focusing on botulinum toxin treatment-naïve patients, only 64 (11.92%) were re-treated at T_3, and 178 (33.14%) at T_4, suggesting a longer duration in treatment-naïve patients, as confirmed by the PGA assessment that showed satisfactory results at 6 months in nearly 75% of the treatment-naïve patients.

Physicians reported that aboBoNT-A solution helped to increase the speed of the treatment because there is no need to reconstitute the drug, thus saving time to dedicate to patient.

At T_3 and T_4 a total of 201 (37.08%) patients were treated with both liquid abobotulinum toxin on the glabellar area and a hyaluronic acid filler in the lower central face and middle third according to the centrifugal technique approach [10, 11].

Remarkably, at T_3 and T_4, physicians injected glabella with a three-point technique, decreasing the total botulinum toxin dose from 50 units (10 units × 5 points) to 21/30 units (7/10 units × 3 points) in 403 (74.35%) patients.

Interestingly, 38 patients had a family history of autoimmune diseases and did not experience any side effects in both the short and long term (24 weeks).

DISCUSSION

Overall, real-life data, collected during the first months of liquid abobotulinumtoxinA availability on the Italian market, confirm the safety, reproducibility, and efficacy profile of the drug for the correction of moderate-to-severe glabellar lines, shown in published RCTs [4, 5]. In particular, our study reports a high level of patient satisfaction for the aesthetic results and a high level of clinical improvement, respectively, by patients and physicians at 48 h after treatment. Duration of the aesthetic results until 6 months was also observed, with 62% of patients requiring re-treatment at 5 months and 38.5% at 6 months. Data presented in relation to patient satisfaction and the rate of touch-ups suggest a decreased inter- and intra-physician variability; in fact steps capable of triggering this variability were diminished (i.e., toxin reconstitution or fixed amount of units). Moreover, the tailored injection device used in our study may have contributed to precision during the injection and avoided dose errors and waste of units. Furthermore, part of the product stays adherent to the vial or to the syringe and the overall amount of injected reconstituted solution could be lower in terms of units.

Syringes not dedicated to botulinum toxin injections also make it difficult to account for the exact number of units injected at a single point. Conversely, aboBoNT-A can be injected with a dedicated device that acoustically reminds the user every time you inject. Future studies are mandatory to compare syringe performance and device influence in terms of inter- and intra-physician reproducibility.

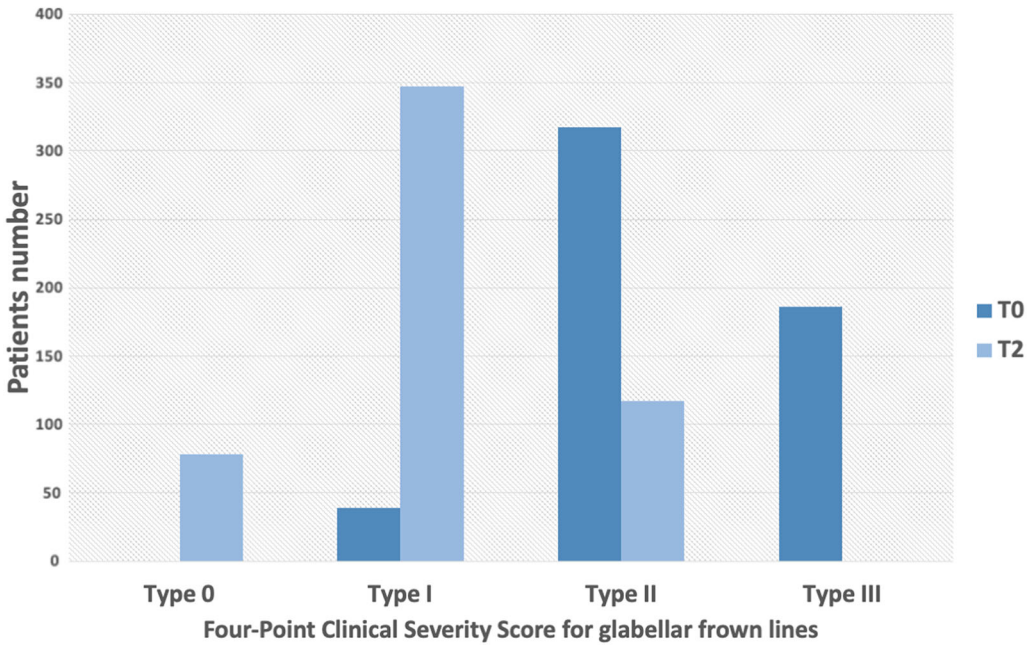

Fig. 1 Histogram comparing glabellar lines severity at T_0 and at T_2

Real-life data also suggest that the ready-to-use aboBoNT-A solution allows to save time (i.e., reconstitution phase skipped) that can be dedicated to the patient for additional aesthetic treatments during the same visit, ensuring optimal patient satisfaction. Furthermore, in our clinical experience, the ready-to-use toxin also represents an easily approachable and synergic treatment to complete the clinical/surgical visit, thus optimizing the overall aesthetic results.

The use of botulinum toxins for aesthetic procedures in the glabellar area is safe and highly appreciated from a patient perspective; aboBoNT-A liquid solution confirms the previous data. In addition, its long-lasting results and low rate of mild side effects at the injection site may consolidate a trustful relationship with the patient, a key point in aesthetic medicine.

Interestingly, real-life data matched RCTs in terms of patient perception at 48 h after the treatment, reinforcing the idea that the new formulation of aboBoNT-A has a fast onset of action and a positively impact on patient satisfaction [4, 5]. Data also highlighted that neither demographic characteristics nor scholarity influenced patient satisfaction and it further indicates that patient counseling during the preliminary visit is of paramount importance to shaping patients' expectations.

Fast improvement and long-term duration can mainly explain the high percentage of patients (98.2%) who declared to be "highly satisfied" compared to the 85% of "satisfied" or "very satisfied" patients reported in the literature [4, 5, 12]. Although assessment scales used in this study are different from those used in RCTs and no direct comparison can be done, in almost 40% of the patients the treatment results lasted for 6 months, a greater percentage of patients compared with the 27% reported in RCTs [4, 5]; these results are of particular interest since our cohort included a high percentage of non-toxin treatment-naïve patients, while only toxin treatment-naïve patients had been included in clinical trials.

Furthermore, injection technique and dose were modified when patients were re-treated. In particular, clinicians almost always decided to switch from the five-point to the three-point injection technique, reducing the overall amount of units injected in both botulinum toxin treatment-naïve and non-treatment-naïve patients, an approach not described in previous

studies. Controlled clinical studies on the efficacy of botulinum toxin at decreasing/lower dose could be of interest, in addition to the existing data with escalating dose [12].

The ready-to-use liquid formulation of aboBoNT-A allows the physician to have an easily available drug that can be used in combination with other aesthetic treatments to further meet patients' needs. In our clinical experience, around 37% of patients treated with the new liquid abobotulinum toxin on the glabellar area also received hyaluronic acid filler treatment in the middle third and lower central face in the same session during the re-treatment (T_3 or T_4).

This study has some limitations concerning the study design (e.g., lack of a control group); however, the objective was to evaluate the safety and efficacy of a widely known active principle supported by a robust literature, currently available on the market also in a liquid, ready-to-use formulation.

CONCLUSION

The liquid toxin is an efficient, durable, reproducible, easy-to-use drug and affords clinicians more time availability (owing to no reconstitution time) that can be used to collect medical data or even to perform additional treatments. From a patient perspective, these data suggest that approximately 50% of the patients treated with liquid aboBoNT-A had a clinically visible effect at 48 h after injection and the effect is maintained until 6 months in approximately 40% of patients.

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Compliance with Ethics Guidelines. The present study received the approval by the Institutional Review Board of San Raphael Hospital (protocol code 178/INT/2021, date of approval 10 November 2021, post hoc analysis). All subjects signed a consent form.

Disclosures. Carlo Di Gregorio, Matteo Tretti-Clementoni, Magda Belmontesi, Marina Romagnoli, Alessandro Innocenti, Malvina Zanchi, Lucia Leone, Giovanni Damiani, Ivano Iozzo have nothing to disclose.

(Contributor Roles Taxonomy) Author Statement. All authors contributed equally.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Flynn TC. Advances in the use of botulinum neurotoxins in facial esthetics. J Cosmet Dermatol. 2012;11:42–50.

2. Li X, Sui C, Xia X, Chen X. Efficacy and safety of botulinum toxin type A for treatment of glabellar lines: a network meta-analysis of randomized controlled trials. Aesthetic Plast Surg. 2022. https://doi.org/10.1007/s00266-022-03018-y.

3. Anido J, Arenas D, Arruabarrena C, et al. Tailored botulinum toxin type A injections in aesthetic medicine: consensus panel recommendations for treating the forehead based on individual facial anatomy and muscle tone. Clin Cosmet Investig Dermatol. 2017;10:413–21.

4. Hilton S, Kestemont P, Sattler G, et al. Liquid abobotulinumtoxinA: pooled data from two double-blind, randomized, placebo-controlled phase III studies of glabellar line treatment. Dermatol Surg. 2022;48(11):1198–202.

5. Ascher B, Kestemont P, Boineau D, et al. Liquid formulation of abobotulinumtoxinA exhibits a favorable efficacy and safety profile in moderate to severe glabellar lines: a randomized, double-blind, placebo- and active comparator-controlled trial. Aesthet Surg J. 2018;38(2):183–91.

6. Damiani G, Calzavara-Pinton P, Stingeni L, et al. Italian guidelines for therapy of atopic dermatitis–adapted from consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis). Dermatol Ther. 2019;32(6):e13121.

7. Damiani G, Alessandrini M, Caccamo D, et al. Italian expert consensus on clinical and therapeutic management of multiple chemical sensitivity (MCS). Int J Environ Res Public Health. 2021;18(21):11294.

8. Brohede S, Wingren G, Wijma B, Wijma K. Validation of the body dysmorphic disorder questionnaire in a community sample of Swedish women. Psychiatry Res. 2013;210(2):647–52.

9. Honeck P, Weiss C, Sterry W, Rzany B, Gladys study group. Reproducibility of a four-point clinical severity score for glabellar frown lines. Br J Dermatol. 2003;149(2):306–310.

10. Di Gregorio C, Rogers J, D'Arpa S. Hyaluronic acid-based two-stage medical therapy to unfold the aged face: the centrifugal approach. J Cosmet Dermatol. 2021;20(3):798–803.

11. Monheit GD, Baumann L, Maas C, Rand R, Down R. Efficacy, safety, and subject satisfaction after abobotulinumtoxinA treatment for moderate to severe Glabellar lines. Dermatol Surg. 2020;46(1):61–9.

12. Dayan S, Joseph J, Moradi A, et al. Subject satisfaction and psychological well-being with escalating abobotulinumtoxinA injection dose for the treatment of moderate to severe glabellar lines. J Cosmet Dermatol. 2022;21(6):2407–16.