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Effectiveness of botulinum neurotoxin type A injections in naïve and previously-treated patients suffering from Torti- or Laterocollis or -caput: Results from a German-Austrian open-label prospective post-marketing surveillance study

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ABSTRACT

AbobotulinumtoxinA (aboBoNT-A; Dysport®) is an effective treatment for cervical dystonia (CD) with a well-established safety profile. In this prospective, multicentre, non-interventional study (NCT01840462) the primary objective was effectiveness (Tsui score) of aboBoNT-A in botulinum neurotoxin type A (BoNT-A) treatment-naïve and previously-treated (> 2 yrs) patients after two injection cycles (at visit 3). Secondary objectives included the effectiveness of aboBoNT-A overall visits and quality of life (CDQ-24) in different CD subtypes. Observation time was 12–16 months, including 5 visits and 4 injection cycles (each 3–4 months). In the analysis population 273 patients from 41 centres across Germany and Austria were included. At baseline, 62.6% were previously-treated with BoNT-A. The major primary components of CD were torticollis (64.5%) and torticaput (17.6%). Previously-treated patients showed a slight reduction of the Tsui scores, whereas BoNT-A-naïve patients had a more severe baseline Tsui score and improved much more over all cycles. Results were similar for CDQ-24. Interestingly, improvements mainly occurred in the Tsui subscore A (amplitude of sustained posture). Marked differences between CD subtypes regarding effectiveness could not be determined. To our knowledge this is the first large multi-centre study investigating the effectiveness of BoNT-A in different primary subtypes of CD over several injection cycles.

1. Introduction

Cervical dystonia (CD) is a widespread form of focal dystonia with an estimated overall prevalence of 50 cases per million [1]. Idiopathic CD is characterised by involuntary contractions of specific muscles resulting in abnormal head movements and various undesired postures of the head. This is associated with symptoms of pain in the neck and shoulder region, decreased range of motion and impairment of voluntary movement of the head with forced positions and possible hypertrophy of the affected muscles. Depending on the direction of movement of the head the disorder is referred to as rotational torticollis (turning of the head/deviation in transversal plane), laterocollis (tilting of the head to the side/deviation in frontal plane) and antero- or retrocollis (inclination of the head to the front or the back/deviation in sagittal plane). Further differentiation of this classification into -collis and -caput subtypes is relevant in clinical practice because these malpositions have their root cause at different levels of the spine (between C3 and C7 or above C3 respectively) thus affecting different groups of muscles and influencing treatment strategy [2,3].

Botulinum neurotoxin type A (BoNT-A) is used for targeted muscle

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relaxation in various diseases, such as focal dystonias and spastic movement disorders [4,5]. Since efficacy and safety of BoNT-A for the treatment of CD has been demonstrated in multiple randomised placebo-controlled trials [6–9], international practice guidelines recommend BoNT-A as first-line treatment for CD [10]. Furthermore, a large open prospective study confirmed safety and effectiveness of the BoNT-A abobotulinumtoxinA (aboBoNT-A) in treatment-naïve patients presenting with heterogeneous forms of CD, when using a standardised regimen that allows tailored dosing based on individual symptom assessment [11]. In addition, improvements in quality of life up to 12 weeks after injection were observed [12,13]. However, data on the long-term use of BoNT-A or on its use in previously-treated patients are scarce, especially in a real-world setting. Hence, the present study was conducted to investigate the effectiveness of aboBoNT-A in BoNT-A-naïve as well as in previously-treated patients with CD over 12 months in a real-world non-interventional setting following the clinical routine. Analyses included stratification by primary component of CD (torticollis, torticaput, laterocollis or laterocaput).

2. Material and methods

2.1. Study design and patients

This was a prospective, open-label, non-interventional multi-centre post-marketing surveillance study, conducted at 41 sites in Germany and Austria (NCT01840462). The study design was reviewed and approved by the Independent Ethics Committee/Institutional Review Board as applicable in the country and is consistent with the ethical standards included in the Declaration of Helsinki of 1964 and its later amendments. Male and female patients aged 18 years or older suffering from CD with torticollis/−caput or laterocollis/−caput as the primary component, intended to receive or already receiving treatment with aboBoNT-A (Dysport®, Ipsen Pharma GmbH) were eligible for inclusion. Patients could be either naïve to BoNT-A (BoNT-A-naïve) or previously-treated with BoNT-A (previously-treated) on a regular basis for at least 2 years prior to inclusion whereby the last aboBoNT-A injection was between 3 and 6 months prior to inclusion. Patients were excluded if they suffered from anterocollis or retrocollis as primary component. All patients were required to provide their written informed consent prior to enrolment. The observation period comprised 12–16 months, including 5 visits.

2.2. Study treatment

The decision to prescribe aboBoNT-A was made by the treating physician independently from the decision to enrol the patient and in accordance with the locally applicable Summary of Product Characteristics (SmPC). Study visits included an inclusion visit (V1) and three follow-up visits (V2, V3 and V4) 3 to 4 months, 6 to 8 months and 9 to 12 months, respectively, after V1. A last visit at the end of the study (V5) was scheduled approximately 12 weeks after V4. The V1 (baseline) procedures included obtaining informed consent, eligibility check, review of demographics, medical history (including CD history and concomitant diseases) and previous CD treatment with BoNT-A, determination of primary and secondary component of CD, assessment of TSUI score and QoL (CDQ-24) as well as treatment with aboBoNT-A. The V2 to V4 procedures included assessment of TSUI score, treatment with aboBoNT-A and reason(s) for discontinuation, if applicable. At V3 the QoL (CDQ-24) was reported, too. The V5 procedures included assessment of TSUI score and QoL (CDQ-24) and reason(s) for discontinuation. All of the procedures performed at these visits were in accordance with routine clinical practice. To ensure that data collected reflect the current clinical practice, the investigators were free to choose the targeted muscles, dosage, and the number of injection sites. In accordance with the SmPC, the injections of aboBoNT-A were expected to take place every 3–4 months.

2.3. Assessments

The primary objective was to evaluate the effectiveness of aboBoNT-A in CD after 2 injection cycles in BoNT-A-naïve and previously-treated patients (V3 compared to V1 (baseline)). Effectiveness was measured by the change of severity of CD on the validated Tsui rating scale. The Tsui score (0–25 points) measures functional aspects of CD (amplitude of rotation, deflection and ante-/retrocollis (subscore A), the duration of movement (subscore B), severity and duration of shoulder elevation (subscore C), severity and duration of tremor (subscore D), whereby a high score reflects a severe condition [14]). Secondary objectives included the effectiveness measures at each visit compared to baseline (V2, V4, V5). Moreover, quality of life (QoL) was assessed using the Craniocervical Dystonia Questionnaire CDQ-24 at baseline, V3 (after 2 injection cycles) and end of study (V5). The CDQ-24 (range from 1 to 100; 100 reflecting the worst possible QoL) is a disease-specific QoL instrument designed to demonstrate the influence of an intervention on the QoL in CD patients, taking account of stigma, emotional well-being, pain, activities of daily living, and social/family life [15]. Adverse events were documented continuously throughout the study.

2.4. Safety assessment

Adverse Events were not collected in the clinical database. Investigators were asked to report any related adverse event (AE) to the product, non-serious or serious, and any not related serious AE independent of the circumstances or suspected cause. The AE reports were sent by the investigator to the pharmacovigilance department. Safety data collected were reviewed as part of signal detection.

2.5. Statistical analyses

Descriptive statistical analysis of all collected data was performed using SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA). Data presented here refer to the main analysis population (MAP), which comprised all patients who received aboBoNT-A treatment at least once, who had a Tsui score at baseline and V3, and who could be assigned to one of both patient populations (BoNT-A-naïve or previously-treated patients). Confirmatory analyses were performed on the modified MAP (patients of the MAP who had no major protocol deviations) and the complete analysis population (CAP; patients of the MAP who completed all study assessments). Subgroup analyses included stratification by BoNT-A previous-treatment status and primary component of CD. The exploratory statistical analysis of the primary effectiveness variable was conducted by means of a general model for analysis of covariance (ANCOVA), incorporating the total Tsui score at V1 as covariate and the BoNT-A previous-treatment status (previously-treated, naïve) and the primary component of CD (torticollis, torticaput, laterocollis, laterocaput) as fixed between-group factor. Two-sided 95%-confidence intervals and the corresponding *p*-values for within- and between-group treatment differences of the adjusted means (least square means) were provided from the ANCOVA model.

3. Results

3.1. Patient disposition and demographic characteristics

In total, 361 patients from 41 sites were enrolled in the study. One patient did not receive any aboBoNT-A injection and 59 withdrew from the study prematurely. The reasons for withdrawal are presented in Table 1. The MAP, MMAP and CAP comprised 273, 233 and 236 patients, respectively. Baseline demographics for the MAP are summarised in Table 2. The majority of patients of the MAP (176 patients (64.5%)) suffered from torticollis as primary CD component. Moreover, the MAP included 171 (62.6%) previously-treated and 102 (37.4%) treatment-naïve patients. Concomitant diseases were reported for 107 (39.2%)

Table 1
Reasons for drop-out (multiple answers possible).

Reason	N
Lost to follow-up	11
Withdrawn consent	9
Insufficient efficacy	8
Insufficient compliance	5
Discontinuation of aboBoNT-A after assessment of the investigator	3
Death	3
Other unstated reasons	32

Table 2
Baseline demographics.

Parameter	N = 273
Primary component of CD, n (%)	
Torticollis	176 (64.5%)
Torticaput	48 (17.6%)
Laterocollis	30 (11.0%)
Laterocaput	19 (7.0%)
Secondary component of CD, n (%)	
Torticollis	26 (12.7%)
Torticaput	27 (13.2%)
Laterocollis	30 (11.0%)
Laterocaput	19 (7.0%)
No secondary component	30 (14.6%)
Not specified	68 (24.9%)
BoNT-A previous-treatment status, n (%)	
Previously-treated	171 (62.6%)
Treatment-naïve	102 (37.4%)
Age (years), mean ± SD (range)	56.8 ± 12.7 (24–85)
Females, n (%)	168 (61.5%)
BMI (kg/m^2), mean ± SD (range)	25.6 ± 3.9 (17.4–46.4)
Duration of CD (years), mean ± SD (range)	8.0 ± 8.3 (0.0–39.8)
Concomitant diseases (incidence > 2%), n (%)	
Any	107 (39.2%)
Hypertension	29 (10.6%)
Diabetes mellitus	15 (5.5%)
Depression	9 (3.3%)
Hypothyroidism	9 (3.3%)

BoNT-A, botulinum neurotoxin type A; BMI, body mass index; CD, cervical dystonia; SD, standard deviation.

patients, most frequently hypertension (10.6%).

3.2. Treatment and dosing

Patients previously treated with BoNT-A had at baseline a mean (± SD) treatment duration of 10.4 ± 5.7 years. Before study start for the majority of patients (73.1%) BoNT-A was injected in 3, 4 or 5 muscles. The mean (± SD) overall dose for the last aboBoNT-A administration before study start was 645.6 ± 252.6 units (range 80–1400 units). The frequency distribution of injected muscles for the first aboBoNT-A administration within the study is shown in Fig. 1. For the treatment and dosing we only describe trends since no statistics have been performed here. Of note, Musculus obliquus capitis inferior was injected in 9.9% of patients in total, whereas 14.7% of BoNT-A-naïve patients compared to 7.0% of previously-treated patients received injections into this muscle. In total, the mean (± SD) number of injected muscles was 3.8 ± 1.4 at V1 and remained constant in the course of the study. This was similar throughout all CD subtypes. However, while the mean number of injected muscles was constant in the course of the study for previously-treated patients, there was an increase from 3.4 ± 1.4 muscles at V1 to 3.7 ± 1.3 at V2 and 3.8 ± 1.4 muscles at V4 for BoNT-A-naïve patients. Dose modifications in the course of 4 injection cycles were performed in 65.6% of patients, with modifications in 53.9% of previously-treated and 86.8% of BoNT-A-naive patients. In total, the overall mean (± SD) dose at V1 was 598.8 ± 260.2 units. It slightly increased until V3

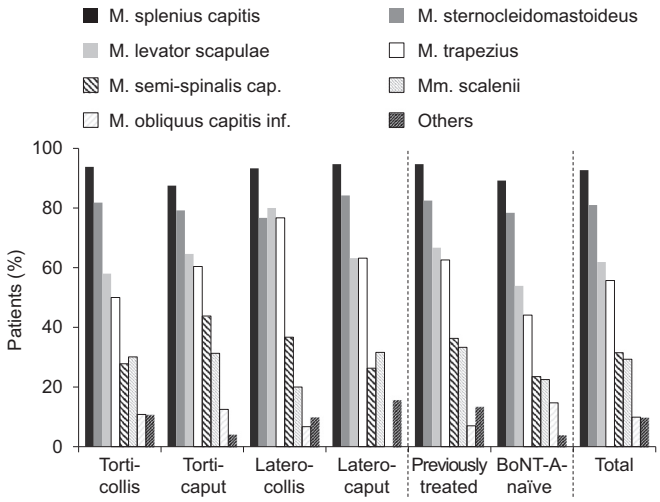

Fig. 1. Injected muscles for first BoNT-A administration overall and by primary component of CD and BoNT-A previous-treatment status.

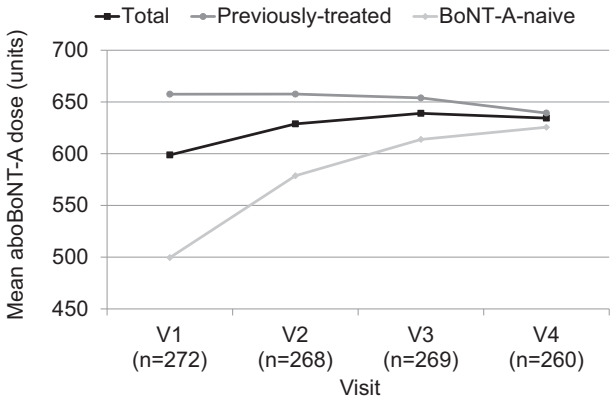

Fig. 2. Mean aboBoNT-A dose applied during the course of the study. Stratified by previous-treatment status. aboBoNT-A, abotulinumtoxinA.

(639.0 ± 246.0 units) and remained at this level (V4: 634.4 ± 265.3 units) (Fig. 2). This trend also applies to the four components of CD. On average, previously treated patients received a higher aboBoNT-A dose than BoNT-A-naïve patients at V1 (657.5 ± 246.0 units vs. 499.6 ± 254.4 units). While the mean aboBoNT-A dose was maintained on a stable level in the course of the study for previously-treated patients, there was an increase in the mean aboBoNT-A dose via 578.7 ± 285.7 units at V2 to 625.6 ± 304.7 units at V4 for BoNT-A-naïve patients, resulting in comparable mean dose levels at V4 for previously-treated and BoNT-A-naïve patients (Fig. 2).

3.3. Effectiveness results

At baseline, the mean (± SD) overall total Tsui score was 6.4 ± 3.8. Similar Tsui scores were documented for patients with torticollis and torticaput (6.4 ± 3.8 and 6.5 ± 3.7 points) as primary component of CD, respectively. Patients with laterocollis and laterocaput as primary component of CD, respectively, had the lowest and highest mean values (5.7 ± 3.5 and 7.2 ± 4.6). BoNT-A-naïve patients had a considerable higher mean total Tsui score at baseline compared to previously-treated patients (7.8 ± 4.2 vs. 5.6 ± 3.3). Changes in the Tsui score from baseline during the study are shown in Fig. 3. Overall, the mean change of the total Tsui score from V1 to V3 (primary effectiveness variable) was −1.2 ± 3.4. There were no marked differences between primary components of CD (torticollis: −1.1 ± 3.6, torticaput: −1.4 ± 3.6, laterocollis: −0.9 ± 2.7,

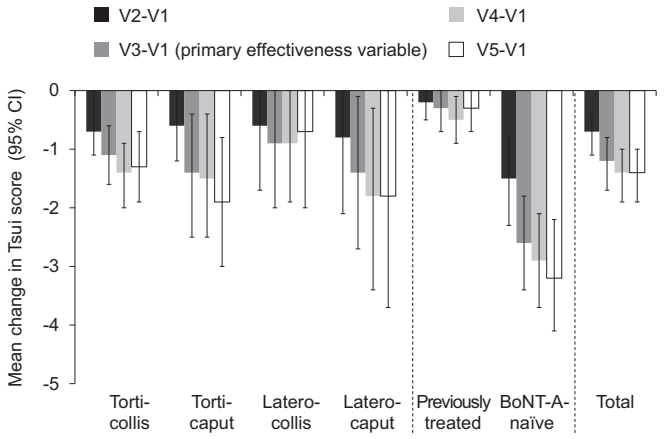

Fig. 3. Changes in the total Tsui score from baseline. Bars represent the 95% confidence interval.

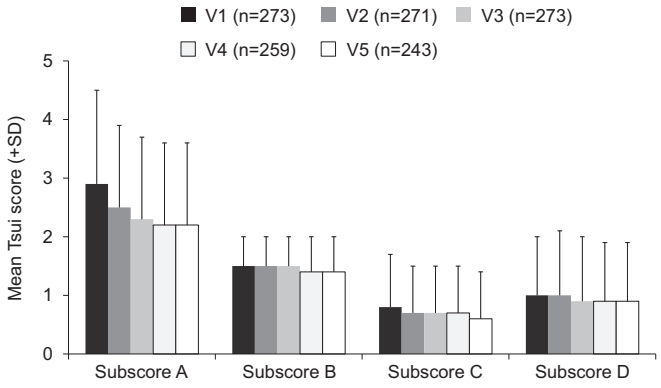

Fig. 4. Tsui subscores over the course of the study. Subscore A (range 0–9 points): amplitude of rotation, deflection and ante-/retrocollis; Subscore B (range 1–2 points): duration of movement (1 = intermittent, 2 = constant); Subscore C (range 0–3 points): severity and duration of shoulder elevation; Subscore D (range 0–4 points): severity and duration of tremor.

laterocaput: −1.4 ± 2.7). However, BoNT-A previous-treatment status had a marked impact on change from V1 to V3 in the total Tsui score (−0.3 ± 2.4 for previously-treated patient vs. -2.6 ± 4.3 for BoNT-A-naïve patients). This difference between the patient groups was statistically significant. Exploratory statistical analyses of the primary effectiveness variable by means of an ANCOVA model, incorporating the total Tsui score at V1 as covariate and the BoNT-A previous-treatment status and the primary component of CD as fixed between-group factors (model 1) showed statistically significant effects of BoNT-A previous-treatment status ($p = .0010$) and total Tsui score at V1 ($p < .0001$). In addition, two separate ANCOVA models (including both fixed between-group factors) were applied incorporating also the interaction terms total Tsui score at V1 x primary component of CD (model 2) and total Tsui score at V1 x BoNT-A previous-treatment status (model 3), respectively. Model 3 confirmed a statistically significant interaction between both variables ($p < .0001$), however, the effect of primary component of CD (model 1) and the interaction between the total Tsui score at V1 and the primary component of CD (model 2) were not statistically significant. These results led to a post-hoc ANCOVA model (without primary component of CD), incorporating the total Tsui score at V1 as covariate and the BoNT-A previous-treatment status as fixed between-group factor as well as the interaction term total TSUI score at V1 x BoNT-A previous-treatment status. The BoNT-A previous-treatment status, the total Tsui score at V1 and the interaction between both variables were statistically significant. The adjusted mean change from V1 to V3 was −0.5 points (95% CI (−0.9)–(−0.1)) for previously-treated patients and −1.6 points (95% CI (−2.1)–(−1.1)) for BoNT-A-naïve patients (difference between adjusted means: 1.1 points (95% CI 0.4–1.7)). The difference between adjusted means increased with increasing total Tsui score at V1, reflecting that BoNT-A-naïve patients with high total Tsui score levels had the greatest Tsui score reduction by aboBoNT-A treatment (difference between adjusted means for 9 points at V1: 2.1 points (CI 95% 1.3–2.9), 5 points at V1: 0.5 points (CI 95% (-0.3)–1.2), 4 points at V1: 0.1 points (CI 95% (-0.8)–0.9)).

Taken together there is a marked difference of the Tsui score at baseline being lower meaning better in the previously-treated group possibly due to the residual effect of the BoNT treatment compared to the BoNT-A-naïve group. Moreover, the higher the Tsui score at baseline the higher the difference from baseline to V3. The Tsui score was significantly stronger reduced in the BoNT-A-naïve group compared to the previously-treated group at V3. No significant difference could be determined in change of Tsui score between the different CD subtypes.

The analysis of change in Tsui score between baseline and all other single observation time points showed similar trends as described above (Fig. 3). The overall improvement of Tsui score after the first injection cycle (at V2) was less pronounced (−0.7 points). At the subsequent visits the difference of Tsui score improved subsequently up to −1.4 points. Stratification by neck and head subtypes (−collis and -caput) showed slight improvements of the Tsui score over the study in all subtypes, but there was no advantage for one or another subtype in any cycle. Previously-treated patients remained within a moderate range of Tsui score changes, with a minimal difference of -0.2 points at V2 (n = 171) and a maximum difference of -0.5 points at V4 (n = 154), while BoNT-A-naïve patients showed continuous improvement after the first injection cycles, almost reaching a stable level at the end of the observation period. The differences of the Tsui score improved from -1.5 points at V2 (n = 100) to -3.2 points at V5 (n = 89).

The observed changes in the total Tsui score are driven by the changes of the Tsui subscore A (amplitude of rotation, deflection and ante-/retrocollis) (Fig. 4). Mean values of subscores B, C and D remained mostly stable over the course of the study (Fig. 4). Analyses by primary component of CD showed no clear trend for Tsui subscores in the course of the study. In contrast, analyses by BoNT-A previous-treatment status revealed that differences between previously-treated and BoNT-A-naïve subjects in the total Tsui score at V1 and in the change from V1 to V3 were primarily due to the Tsui subscore A (V1: 2.4 ± 1.4 vs. 3.6 ± 1.6; V3-V1: -0.1 ± 1.1 vs. -1.2 ± 1.7).

The mean (± SD) overall CDQ-24 total score at baseline was 32.5 ± 18.6. For all four primary components of CD the mean CDQ-24 total scores at V1 were of comparable size, ranging from 31.7 ± 18.5 for torticaput to 33.8 ± 17.0 for laterocaput. BoNT-A-naïve patients had a considerably higher mean CDQ-24 total score at V1 compared to previously-treated patients (38.4 ± 17.6 vs. 28.9 ± 18.2). Over the course of the study, the overall CDQ-24 total score decreased from baseline to V3 and V5 by 4.7 ± 14.4 and 4.8 ± 15.5 points, respectively, indicating slight improvement in all patients (Fig. 5). Previous-treatment status had a marked impact on change of the CQD-24 total score. That of BoNT-A-naïve patients clearly improved during the observation period (by 8.2 ± 15.1 at V3 and by 10.2 ± 16.8 at V5), while the score of previously-treated patients showed only a minimal improvement (by 2.6 ± 16.6 at V3 and by 1.8 ± 13.9 at V5), remaining at the level of the baseline visit. As described for the Tsui score the previously-treated patients start at a lower meaning better CDQ-24 score compared to BoNT-A-naïve patients possibly indicating the carry-over effect of the BoNT-A pretreatment when visits take place (3–4 months post injection).

At V3, head-subtypes (torti- or laterocaput) had smaller mean changes when compared with neck subtypes (torti- or laterocollis). However, at V5, the results stratified by primary component of CD varied considerably between the single subtypes so that no tendency with respect to the primary component of CD could be identified.

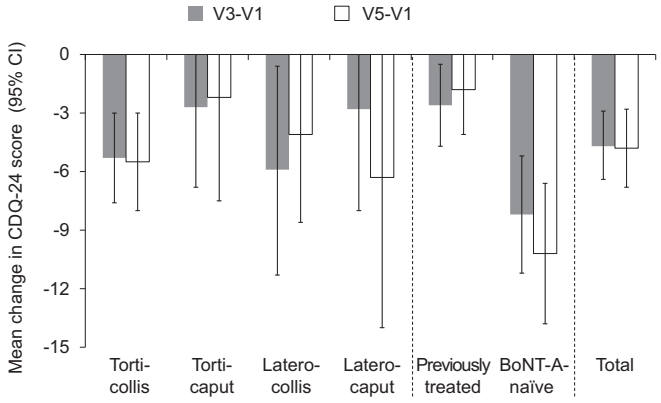

Fig. 5. Changes in the CDQ-24 score from baseline. Bars represent the 95% confidence interval.

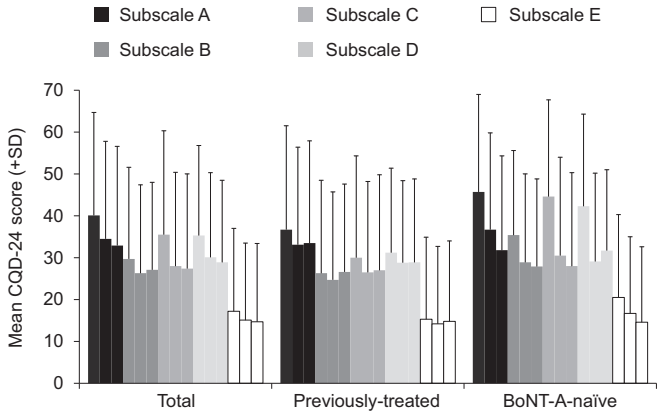

Fig. 6. CDQ-24 subscales over the course of the study. Values were obtained at V1, V3 and V5, respectively. Subscale A: Stigma, Subscale B: Emotional well-being, Subscale C: Pain, Subscale D: Activities of daily living, Subscale E: Social/family life.

The highest mean values at V1 are mirrored in the subscales stigma (40.1 ± 24.6), pain (35.5 ± 24.8) and activities of daily living (35.3 ± 21.5). The subscales emotional well-being and social/family life had lower mean values, thus reflecting better QoL. The subscales stigma, pain and activities of daily life also show the most marked mean changes from baseline (Fig. 6). Mean changes from baseline were less pronounced for subscales.

emotional well-being and social/family life. Analyses by primary component of CD showed no clear trend for CDQ-24 subscales in the course of the study. However, analyses by BoNT-A previous-treatment status showed that differences between previously-treated and BoNT-A-naïve patients in the CDQ-24 total score at V1 and subsequent changes from baseline are reflected in all subscales, however less pronounced in the subscale social/family life (Fig. 6).

Results from the MMAP and CAP pertaining to changes in Tsui score, CDQ-24 score and dose modification were consistent with the MAP.

3.4. Safety results

In total, 15 of 361 patients experienced 31 adverse events (AEs) during the study. Seven of the patients experienced 11 serious adverse events; thereof 5 SAEs (2× dysphagia, 2× muscular weakness, 1× dyspnoea) were evaluated by the investigators as related to the study medication occurring in 2 patients. In these affected patients the dose was reduced or the treatment discontinued. 6 SAEs were evaluated (concussion, chest injury, fall, muscular weakness, septic shock, asphyxia) as not related. Three patients died during the study and were assessed as not related to aboBoNT-A and due to patient's concurrent medical conditions. Of the 20 non-serious AEs (11 patients), 13 AEs were evaluated by the reporter as related to the administration of aboBoNT-A. The most frequently reported adverse reactions were dysphagia (n = 7) and local muscular weakness (n = 5).

4. Discussion

This multicentre, non-interventional, prospective, longitudinal study investigated the effectiveness of aboBoNT-A injections over a period of 12–16 months in BoNT-naïve and previously-treated patients suffering from CD. To the best of our knowledge this was the first study to incorporate the collis/caput classification and to analyse all efficacy variables stratified by primary subtype of CD [2,3]. The primary effectiveness variable was the difference of the Tsui score between baseline and visit 3 (3–4 months between each injection cycle) in BoNT-A-naïve and previously-treated subjects, i.e. after two injection cycles with aboBoNT-A. The evaluation of the primary effectiveness variable showed a slight overall improvement of functional parameters of CD in the main analysis population (after 3–4 months after injection). When looking at the different primary components of CD, torticollis and -caput, laterocollis and -caput, there were no marked differences between these subgroups regarding the Tsui scale. However, caution should be observed with this interpretation because the Tsui score has been criticised for being unable to differentiate between –collis and –caput types of CD [16]. At present, none of the available rating scales reflects this most current conceptual model of CD, indicating a need to develop a rating scale that describes all subtypes of CD [16].

In contrast to the CD subtype, the previous-treatment status had a considerable impact on the change of the Tsui score from baseline to visit 3, which was reflected in the more pronounced change in BoNT-A-naïve compared to previously-treated patients. Furthermore, the higher the Tsui score (i.e. the more severe the condition) was at start of therapy, the more it decreased during the observation period, indicating that the change of the Tsui score is mainly driven by the baseline Tsui score. This effect was mainly due to the BoNT-A-naïve patients. Those with more severe disease at baseline showed the largest improvement during the study, whereas those with a low baseline score did not improve more than previously-treated patients with a similar score. These results indicate that both groups benefit from the treatment with aboBoNT-A. Treatment-naïve patients improve their condition as measured by the Tsui scale, while previously-treated patients, who have already better starting conditions due to a possible carry-over effect of BoNT-A from one visit to the other, maintain or slightly improve their condition. The analysis of the secondary variables, change in Tsui score between baseline and the single observation time points showed similar trends. The stratification by neck and head subtypes (−collis and -caput) showed that the Tsui score improved over the study in all subtypes, but there was no advantage for one or another subtype. In line with the results for the primary variable, there was a marked difference when stratifying into previously-treated and BoNT-A-naïve patients though. The changes in the total Tsui score described above are mainly due to changes in the amplitude of sustained posture. Thus, the clinical effect observed under treatment with aboBoNT-A, is shown mainly on the extent of the malposition of the head and neck, which is one of the main features of CD.

Improving malposition of the head and neck led to improvement in QoL as reflected in the results from the CDQ-24. In line with the Tsui results, BoNT-A-naïve patients clearly improved during the course of the observation period, while previously-treated patients showed only minimal improvement, remaining at the level of the baseline visit which again indicated the carry-over effect of the previous BoNT-treatment that sustains at each visit when patients come back for the injection every 3–4 months. Descriptive analyses showed that results stratified by subtype of CD varied considerably between the single

subtypes. Head-subtypes (torti- or laterocaput) had smaller mean changes between baseline and visit 3 when compared with neck subtypes (torti- or laterocollis), suggesting that patients with neck subtypes may benefit more from the treatment. However, this was not confirmed by the changes between baseline and visit 5. Thus, no advantage for one or another subtype can be deduced from these results. These results are in line with previous findings from an open-label cohort study conducted with BoNT-A-naïve patients in Germany and Austria over 8 weeks [12]. Our findings add to this study by showing the sustained benefits of repeated aboBoNT-A injections up to one year on QoL in BoNT-A-naïve as well as in previously-treated patients. The analysis of the subscales of CDQ-24 shows that the most pronounced changes were observed for the subscales stigma, pain and activities of daily life. It is likely that the obvious malposition of the head and/or neck dimension in the Tsui score has a strong link to the dimension of stigma and pain measured by the CDQ-24 scale. Thus, an improvement of the malposition of the head and/or neck may result in a more active daily life.

The importance of individualised treatment with respect to primary CD subtype has been emphasised before [3,11]. Two registry studies (ANCHOR-CD and CD-PROBE) have recently been published taking the CD subtypes into account [17,18]. From another observational study (INTEREST IN CD2), baseline data have been reported [19]. Whereas these studies describe the primary CD subtypes within the cohort, to our knowledge, this study is the first to evaluate effectiveness over the different subtypes. When the classification of CD into caput and collis subtypes was introduced, new key muscles for BoNT-A injections were proposed, such as M. levator scapulae and *M. obliquus* capitis inferior [20]. The present study shows that these suggestions have been partly implemented into clinical routine. M. levator scapulae was one of the most frequently injected muscles. Injection rates for *M. obliquus* capitis inferior were higher in BoNT-A-naïve patients (~15%) compared to previously-treated patients (7%), indicating that physicians get more familiar with this muscle and new (naïve) patients receive a treatment of that muscle. On the other hand, fewer injections into M. semispinalis cervicis were documented than would have been expected with torticollis being the most common subtype. This finding underlines that further education in the area of identifying muscles involved in the different CD subtypes is necessary with the aim to improve targeted treatment. The observed treatment regimen and dose change in the BoNT-A-naïve groups reflects the current status of aboBoNT-A usage. Treatment adaptation is much more pronounced in BoNT-A-naive than in previously-treated patients. Apparently, during the first two injections an almost maximal effect has been achieved because Tsui scores are not changing as dramatic from V3 to V5 as from V1 to V3. Similarly, for CDQ-24, the largest step occurs between V1 and V3, while changes are still present, but less pronounced afterwards to V5, indicating that a plateau has been reached at V3 already. An explanation can be that dose adaptation takes mainly place between the first and second injection which is displayed by the number of injected muscles and the dosing where the largest change occurs between V1 and V2 when compared to the following visits. This observation underscores that the best treatment regimen is already identified at the second injection and then only slightly changed.

This study is limited by its non-interventional design which allows the identification of associations, but excludes the conclusion of causal relationships. The maximum effect of BoNT-A is usually occurring around 4 weeks post injection [7] meaning that 3–4 months after injection is already at a late stage of the treatment cycle, but due to the non-interventional design, the earlier time point could not be investigated here. The strength of this study is represented by the use of a validated score to measure the functional aspects of CD and a disease specific questionnaire for the assessment of QoL [14,15]. Bias was minimised by enrolling patients in consecutive order rather than by physician's choice. Hence, the study provides a comprehensive view of the effectiveness of aboBoNT-A in the real world setting of CD in Germany and Austria.

5. Conclusion

Overall, the results from this study are in line with the known efficacy profile of aboBoNT-A, showing that both, previously-treated and BoNT-A-naïve patients with CD benefit from treatment with aboBoNT-A. BoNT-A-naïve patients improved up to one year in both, functional aspects and QoL. Previously-treated patients maintained a stable level of functional and QoL aspects during the observation period. BoNT-A-naïve patients with a more severe baseline condition showed the largest improvement during the study, as reflected in the improved Tsui subscore A (amplitude of rotation/deflection). No difference in treatment effect could be detected for the head and neck subtypes of CD, and no new safety findings emerged from this study.

Conflicts of interest and source of funding

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Data Sharing

Where patient data can be anonymised, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

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