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ORIGINAL COMMUNICATION

Treatment of cervical dystonia with abo- and onabotulinumtoxinA: long-term safety and efficacy in daily clinical practice

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Abstract

Introduction Treatment with botulinum toxin A is the evidence-based first-line therapy of cervical dystonia. The aim of this study was to analyze long-term data of the most commonly used products concerning safety and efficacy in a big cohort over decades.

Methods We retrospectively analyzed the treatment data of all cervical dystonia patients in our outpatient clinic having at least three treatment sessions with current onabotulinumtoxinA or abobotulinumtoxinA. The observation period was up to 17 years for onabotulinumtoxinA and 27 years for abobotulinumtoxinA. We report on safety and efficacy, comparing parameters such as dose, treatment intervals, side effects, occurrence and reasons of primary or secondary non-response.

Results We analyzed a total of 2592 and 6660 treatment sessions in 135 patients with onabotulinumtoxinA, 209 with abobotulinumtoxinA and 10 having received both preparations. We found a moderate increase of dosage in the first years which was succeeded by a stable mean dose (138 and 663 mouse units, respectively) and stable injection intervals from the beginning. The most frequent side effects were mild dysphagia (2/6%), muscle weakness (2/6%) and pain (2/2%). Reasons for therapy discontinuation were change to a nearby doctor, age, other diseases, spontaneous improvement, side effects or possible treatment failure. Of all patients, only two tested positive for neutralizing antibodies against botulinum toxin A.

Conclusion We show that treatment of cervical dystonia with the two most frequently used botulinum toxin A preparations is a safe and effective therapy even over a long treatment duration of up to 27 years.

Keywords Cervical dystonia · AbobotulinumtoxinA · OnabotulinumtoxinA · Long-term treatment · Botulinum toxin A

Introduction

Cervical dystonia (CD) is the most frequent focal dystonia [1] and is characterized by a phasic or tonic abnormal posture of the neck, sometimes accompanied by tremor [2]. It can also be part of a segmental or generalized dystonia with dystonic symptoms in other body regions [2] and be inherited, idiopathic or acquired. Aside from their motor symptoms, CD patients often suffer from relevant pain, social stigmatism and depression [3]. As a chronic condition with a mean age of about 45 years at onset (even younger in many patients with tardive dystonia) [1], CD requires a safe and effective long-term treatment. Here, injections with botulinum toxin (BoNT) are considered as symptomatic first-line therapy [2]. A large number of CD studies have demonstrated the safety and efficacy of BoNT-A, but they differed from our trial in important features. Most of these long-term studies concentrated on only one BoNT-A

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product [4–13], compared small cohorts [14, 15], included patients who had been treated with a meanwhile discarded onabotulinumtoxinA formulation [16, 17] or mixed cohorts from different hospitals [18].

The aim of our retrospective analysis was to reflect current real-life treatment of CD over a long-time course. We included a collective of patients that was heterogeneous in etiology and dystonia distribution, and analyzed treatment with the two most frequently used BoNT-A products, abobotulinumtoxinA (ABO) and onabotulinumtoxinA (ONA). The present ONA-formulation (introduced in Germany in 2000) has a lower content of complexing proteins than the former formulation and thereby decreased antigenicity [19].

Methods

In our retrospective observational study, we included data from each CD patient who was treated at least three times with each ABO or ONA in our movement disorder outpatient clinic between 31/May/1989 and 31/Dec/2016. The study has been approved by the local ethics review board. Some data of the first few treatment years of 100 of the ABO patients had already been reported previously [5].

The treating physician in the outpatient clinic usually changed after ≥ 9 months. During each visit he/she routinely documented the current status including dominating symptom, treatment success according to the patient's statement, duration of action and side effects. Additionally, in a schematic drawing of the cervical anatomy, the topographical distribution of injected BoNT-A units, total volume, dose, batch number, BoNT product and dilution were recorded. Usually, a dilution of 500 mouse units (MU) ABO or 100 MU ONA per 1.0 ml of 0.9% sodium chloride solution was used. The usual volume per injection site was 0.1 or 0.2 ml. Except for deep cervical muscles such as the obliquus capitis inferior muscle, palpation was generally the preferred method of targeting. Furthermore, documentation included tests for treatment failure by anti-BoNT-antibodies determination or by an extensor digitorum brevis (EDB) test. The decision to conduct one of these tests was made by the treating physician without a standardized protocol. If the reason for discontinuation of therapy was not evident from the chart, we retrospectively contacted the patient by phone. Sensory tricks were not systematically documented.

These data and basic information on patient demographics, diagnostic history and previous treatment were extracted from the notes to a database in Microsoft Excel. Side effects were categorized ("dysphagia", "muscle weakness", "pain" or "other side effects") as well as the patient's statement about the treatment success to "good" or "bad/no effect". Statistical analysis was performed using "R" [20].

To test for differences in demographics, *t* tests were used. Differences in injected doses and reported effect duration were assessed by calculating the mean dose/reported duration in the individual's first and fifth treatment year and by employing one-sided paired *t* tests for ABO and ONA separately. Data on the mean dose, duration of treatment effect, satisfaction with therapy and side effects were summarized to descriptive statistics. To assess changes in dose and effect duration, we calculated each patient's mean dose and effect duration per treatment year. For illustrative purposes, a smoothing spline was calculated using the default options in the "R"-package "ggplot2" and shown together with the individual patient's mean (Figs. 1, 2). No statistical tests for differences in therapy-related outcomes for ONA versus ABO were employed due to the complexity of the data set with multiple observations for each subject.

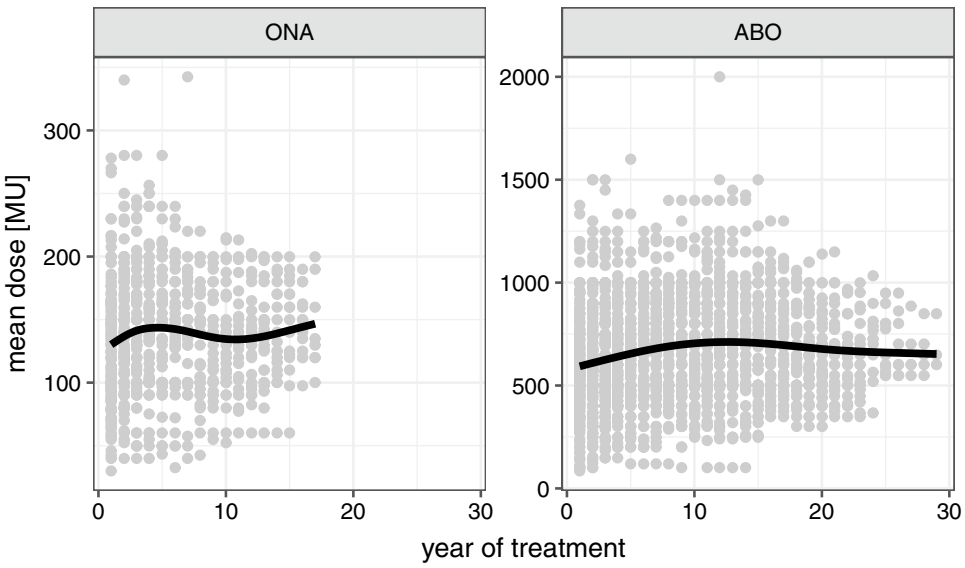

Fig. 1 Mean dose over time. Each dot represents the mean dose a patient received in the respective year of his/her treatment. The dose expressed in mouse units is not interchangeable between ABO and ONA. The line shows the estimate of the average mean dose and its time course as calculated by ggplot2 s default method. *ABO* abobotulinumtoxinA, *ONA* onabotulinumtoxinA, *MU* mouse units

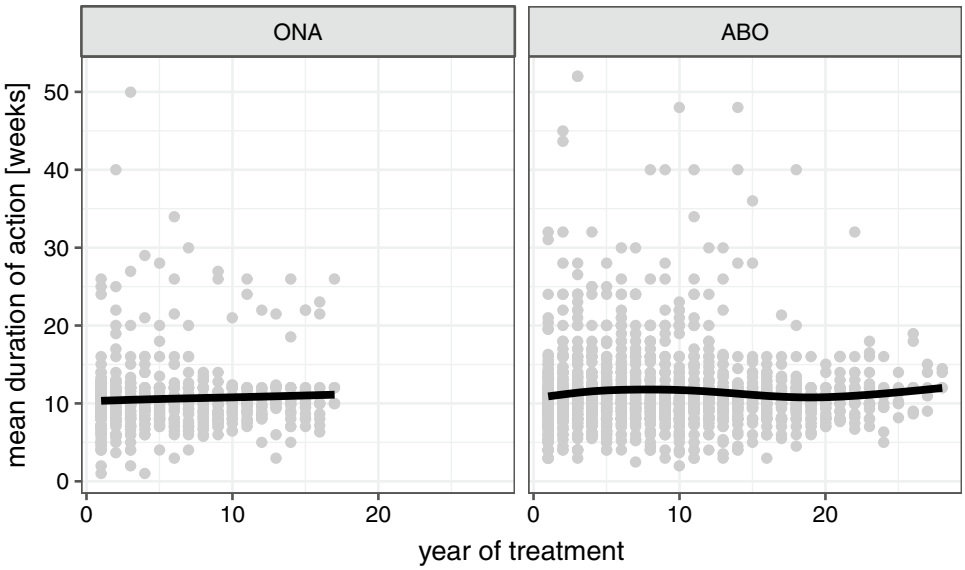

Fig. 2 Effect duration over time. Each dot represents one patient's mean reported effect duration per treatment year in weeks. The line shows an estimate of the average mean effect duration and its time course as estimated by ggplot2s default method. *ABO* abobotulinumtoxinA, *ONA* onabotulinumtoxinA

Furthermore, a post hoc subgroup analysis for the main results was applied regarding the etiology of dystonia. Therefore, we differentiated between patients with non-acquired dystonia (idiopathic and genetic dystonia) versus acquired dystonia (e.g., due to a previous treatment with neuroleptics). Acknowledging the remarkable difference of the group sizes and repeated observations on single subjects, we conducted no statistical tests for this comparison.

Additionally, we analyzed the selection of injected muscles as well as the change of the total dose per treatment in comparison to the previous treatment over the time. Therefore, we calculated the proportion of treatment sessions per year with a stable/increasing/decreasing dose and stable set of injected muscles in comparison to the previous session.

Results

Subjects

In total, data on 334 patients were collected, of which 135 were treated with ONA and 209 with ABO (Supplementary Table 1). The used BoNT-A product was pseudo-randomly chosen. Generally, no switch to another product was performed after the first injection cycle. Ten patients received injections with both preparations in our center, e.g., due to erroneous product selection, lack of stock or following a patient's request. Mean age at disease onset was 46.3 ± 15.3 and 43.7 ± 15.8 years $\pm$ standard deviation, respectively. We included patients with focal CD as well as patients suffering from CD with segmental, multifocal or generalized dystonia (Supplementary Table 2). In terms of etiology, we included patients with inherited or idiopathic dystonia as well as patients suffering from acquired dystonia due to infantile cerebral palsy, intracranial hemorrhage, neurodegenerative disorders or use of neuroleptic medication (Supplementary Table 3). The prevailing diagnosis was idiopathic focal cervical dystonia.

Data on 2592 treatment sessions with ONA and 6660 treatment sessions with ABO were collected. On average, patients have been treated at our clinic for 5.9 ± 5.0 (ONA) and 11.0 ± 7.7 years (ABO). 66% of patients were BoNT-A naïve at the time of their first analyzed treatment. In case of (external) pre-treatment, the previous product was kept with the exception of a small number of cases (14 ONA, 22 ABO). The number of patients previously treated with incobotulinumtoxinA, BoNT type B or several products was negligible (5 ONA, 9 ABO) (Supplementary Table 4). All ONA patients in our study were analyzed starting after the introduction date of the new ONA formulation. Some patients (6 ONA, 8 ABO) had been pretreated with the old ONA formulation. Injected muscles are reported in Supplementary Table 5. The predominant symptom at the beginning of therapy was a torticollis (Supplementary Table 6).

Dosing

The mean total dose per treatment session was 138 ± 51 MU ONA and 663 ± 249 MU ABO with gradual increase in the first years of treatment and stable course afterwards: Dose increased from 124 ± 54 MU (ONA) and 585 ± 254 MU (ABO) in the first year to 144 ± 55 MU (ONA) and 648 ± 240 MU (ABO) in the fifth year of treatment ($p < 0.01$, pairwise t test) (Fig. 1).

Effect duration

The mean reported effect duration was 10.4 ± 8.7 (ONA) versus 10.9 ± 5.4 weeks (ABO) without relevant change over time: the mean effect duration of 10.5 ± 17.6 (ONA) and 10.6 ± 9.6 weeks (ABO) in year 1 was influenced by outliers, as some patients reported a duration of up to 320 weeks. In year 5, the duration was similar as in year 1 for ONA (10.5 ± 3.7 weeks, $p = 0.25$), but significantly longer for ABO than in year 1 with 11.0 ± 3.8 weeks ($p = 0.01$, one-sided pairwise *t* tests) (Fig. 2).

Treatment outcome

Patients reported a satisfactory effect after 86% of all treatment sessions—for both products equally. A majority of patients (ONA: 97/135, ABO 142/209) reported a favorable result after at least 80% of their individual treatments, while only a minority responded less frequently: for 25/135 (ONA) and 21/209 (ABO) patients, a satisfactory effect was achieved in less than 50% of treatments (Fig. 3).

The occurrence of at least some undesired effect was reported after 10% (ONA) and 15% (ABO) of all treatments. The most common side effects were dysphagia occurring in 2% (of all treatment sessions with ONA) versus 6% (ABO), muscle weakness in 2% (ONA) versus 6% (ABO), pain in 2% (each) and other side effects in 4% (ONA) versus 3% (ABO) (Supplementary Table 7). Considering individual patients, 108/135 (ONA) and 147/209 (ABO) reported side effects after less than 20% of their treatment sessions, while a small minority [13/135 (ONA), 7/209 (ABO)] complained about side effects after more than 50% of each subject's sessions (Fig. 3). The occurrence of side effects decreased over time from 17% (ONA) and 21% (ABO) of all treatments in each subject's first year to 6% (ONA) and 14% (ABO) in the fifth year (Fig. 4).

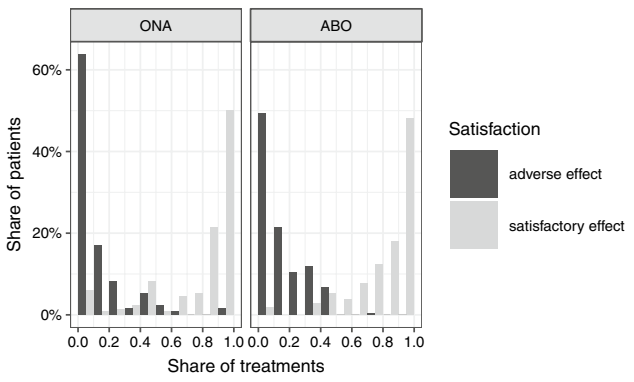

Fig. 3 Portion of treatment sessions with positive effect or side effects. The portion of treatment sessions with positive and negative effect is calculated for each patient. The distribution of outcomes per patient is shown as a histogram. The figure reads for example 50% of all patients treated with ONA reported a satisfactory effect after more than 90% of their injections, and 48% of all patients treated with ABO reported side effects after up to 10% of their injections. *ABO* abobotulinumtoxinA, *ONA* onabotulinumtoxinA

Discontinuation of therapy

59 of 135 patients ever treated with ONA and 100 of 209 ABO patients still remained on therapy in our clinic with the initially chosen product at the end of the observation time. To explore the causes for discontinuation of therapy we differentiated between treatment-associated and other reasons (Table 1). The main motive for treatment-associated therapy termination was treatment failure, which was more often primary treatment failure in ABO patients and secondary in ONA patients. In total, six patients (two ONA, four ABO) were tested for antibodies and eight (three ONA, five ABO) for lack of action using an EDB test. Lack of action was found in two ABO patients who were also tested positive for neutralizing antibodies.

Subgroup analysis regarding the etiology of dystonia

The mean dose was higher considering all treatment sessions of patients with acquired dystonia treated with ABO (713 versus 658 MU) and lower in the ONA group (135 versus 138 MU). Furthermore, effect duration was lower in the acquired group (9.9 versus 10.9 weeks) as was the rate of side effects (11.4% versus 13.3%). A satisfactory outcome was more rarely reported by patients with acquired dystonia

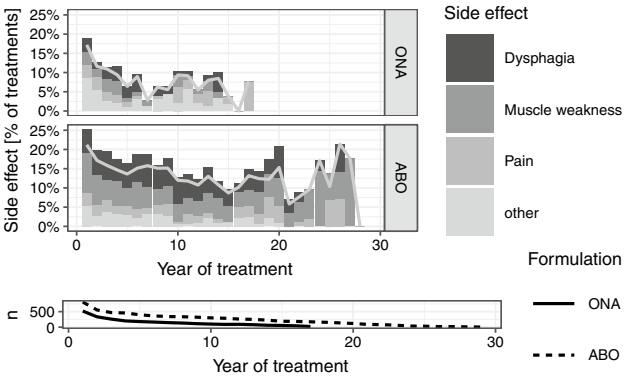

Fig. 4 Side effects. The share of treatment sessions with reported side effects is shown. The line shows the proportion of treatment sessions with at least one side effect. The height of the bars demonstrates the frequency of a specific side effect. "Other side effects" included xerostomia, dizziness, tiredness, hoarseness, mild/subjective dysphagia, rarely headaches and in isolated cases numbness at the injection site. The curves at the bottom demonstrate the number (*n*) of treatment sessions per treatment year for both products separately. *ABO* abobotulinumtoxinA, *ONA* onabotulinumtoxinA, *n* number of treatment sessions

Table 1 Discontinuation of therapy

Reason	ONA (*n*)	ABO (*n*)
No discontinuation	59	100
Unknown reason	19	29
Age	2	5
Concurring disease	4	8
Referral to nearby physician	13	23
Spontaneous remission	4	4
Change of product	10	3
Trial to withdraw	3	5
Side effect	3	7
Referral due to discontent with our department	1	0
Primary treatment failure	12	5
Secondary treatment failure	5	18
Other	0	2

The table shows the number (*n*) of patients who stopped therapy at our center for the given reason

ABO abobotulinumtoxinA, *ona* onabotulinumtoxinA, *n* number of patients

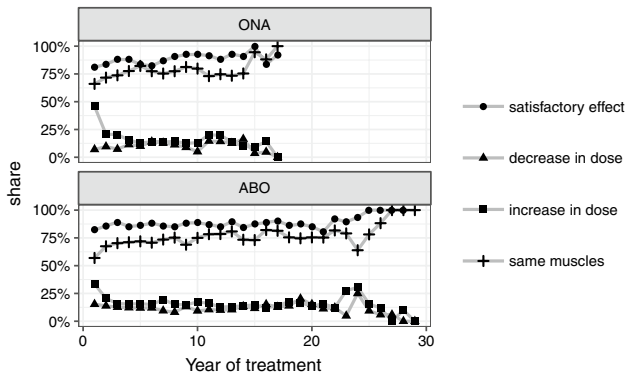

Fig. 5 Development of dose and muscle selection over the time. The share of treatment sessions with an increase or decrease of dose as well as a stable selection of injected muscles in comparison to the previous treatment session is shown for every year of treatment. Additionally, the share of sessions with a satisfactory effect (as reported by the patients) is demonstrated for every year. In the same manner as in Fig. 4, the data for later years of treatment are computed using less treatment sessions (see the lower panel of Fig. 4). *ABO* abobotulinumtoxinA, *ONA* onabotulinumtoxinA

in comparison to patients with non-acquired dystonia (80% versus 87%).

Stability of the dose and muscle selection over the years

As Fig. 5 shows, the proportion of treatment sessions with a stable dose in comparison to its previous session rises over the time from about 50% to roughly 70%. In parallel, a sharp decline of sessions with increased dose can be observed. In the same manner, the proportion of treatment sessions with injections in the same set of muscles as before also rises from year 1 to year 3 from 66 to 73% (ONA) and from 57 to 70% (ABO), respectively. As only data on the total dose and the muscle selection were collected, but not on the dose in individual muscles, a redistribution within the same muscles as treated before could not be detected based on the data entered in the database.

Discussion

Providing the data of 9252 treatment cycles, this study gives insight into long-term BoNT-A therapy of CD. We analyzed a big cohort of patients over a remarkably long treatment duration of up to 27 years. The representative patient cohort was heterogeneous concerning etiology and body distribution of dystonia. All sessions were conducted at the same center by rotational physicians. All this reflects the daily routine at a movement disorder outpatient clinic. The analysis confirmed the efficacy and safety of both ONA and ABO. Acknowledging different cohort characteristics, we compared these products only descriptively. Due to the restriction of the ONA group to patients who had been treated at least three times with the currently used ONA formulation [19], the ONA cohort was smaller (135 patients versus 209 ABO patients) and its mean follow-up time shorter (5 versus 11 years). Previous long-term studies on CD did not differentiate between the two ONA formulations [4, 6, 7, 16, 17], so their results are only partially transferable to the current practice as the old formulation showed less tolerability and a higher antigenicity [19].

Our CD cohort is one of the largest long-term trials on ABO and/or ONA [4, 5, 7–12, 14–18] with the exception of a cohort of 568 CD patients treated exclusively with ABO [21] and another of 234 ONA patients [13], both with a remarkably shorter follow-up period. To the best of our knowledge, a follow-up of 27 years is longer than that of any other published BoNT study on any indication. Focusing on the long-term aspect, we included only patients being treated at least three times with one product subsequently. While many large studies did not use a minimal treatment duration (e.g., [3, 5, 11, 13, 22, 23]), others demanded a minimum of, e.g., four treatment sessions or even a period of 10 years [6, 7, 9, 10, 12, 21, 24]. As we were also interested in the occurrence of treatment failure, we decided against such strict inclusion criteria to avoid a relevant selection bias.

Reflecting usual clinical practice, our cohort was also heterogeneous concerning the CD complexity. About two-third of our patients had CD patterns with at least three different CD components (Supplementary Table 6). These included phasic movements, tremor, antero-/retrocollis and sagittal/lateral shift which complicate treatment [25]. Also, the

frequent change of treating physicians is representative for a tertiary care hospital as well as the relatively high percentage of pretreated patients (34%).

As CD is a chronic condition, the question of a possible tolerance effect of BoNT-A is relevant. Our data show an increase of the mean dose in the first years and then a very stable course over many years. The increase at the beginning of the treatment reflects the strategy of starting with a low dose to avoid side effects and titrating the dose in the following sessions. An increase of dose over the first ten sessions has recently been reported in a smaller group of CD patients treated with ABO [10], and also been discussed as a result of dose titration [14]. Also the selection of injected muscles became very stable from session to session approaching 100% in the last treatment sessions.

Slight fluctuations of the mean doses with the growing number of treatment years in our study can be explained by the increasing standard deviation due to a decreasing number of patients.

The mean dose of 138 MU ONA was lower than in previous long-term studies [7, 9, 24, 26] and also than in the prospective, "real-life", CD PROBE cohort of over 1000 US patients (mean dose 189 MU), though this cohort was comparable with 63% BoNT-naïve subjects [22].

On the contrary, the mean dose of 663 MU ABO was high in comparison to a meta-analysis of 1202 patients' data (500 MU) [25], the exploratory analysis of two open-label extension studies following a 500 MU-fixed-dose trial with 218 patients [27] and in comparison to minor long-term studies (389 MU in 163 [17] or 487 MU in 37 patients [8]). However, some studies reported similar [5, 10] or higher [24] mean doses in long-term treatment.

The effect duration of the injections was very stable over the years (Fig. 2). Acknowledging the retrospective study character with data of 27 years acquired by various physicians, the low scattering of this result is remarkable, especially as the parameter "duration" had not been exactly predefined and patients' questioning had not been standardized. As most patients were retreated before complete reestablishment of CD symptoms, most reported the time after which the optimal effect of the last injection had waned. In the mentioned meta-analysis on ABO for CD, the average effect duration was 12 weeks, whereas the definition of treatment "duration" was heterogeneous in the included trials as well [25]. Two studies reported a longer duration of both the maximal effect and total response, with a trend to an increase over time [7, 10]. This might partly be explained by the exclusion of patients with acquired dystonia [10] or the inclusion of patients with facial dystonia [7], respectively.

Concerning the treatment effect, 86% of all treatment sessions were judged as satisfactory by the patients in both cohorts which was identical to outcome data in previous long-term studies [6]. Most patients were satisfied with more than 80% of their treatments. Notably, these results include all treatment sessions irrespective of whether therapy was stopped afterwards due to a treatment failure or continued due to a good effect. The percentage of satisfying treatment sessions is comparable to findings of other trials [6] with more homogeneous cohorts due to more restricted artificial inclusion criteria.

As usual for retrospective trials, a relevant number of patients stopped the therapy in our center for various reasons. In 71%, these reasons were unknown or not related to the therapy itself, e.g., age or the switch to a doctor closer to home. The percentage of patients who stopped the therapy because of side effects was low (2% of all ONA patients, 3% under ABO). Primary or secondary treatment failure as described by the patients and/or seen by the doctor was the reason to stop therapy for 11.9% of the whole cohort (12.6% ONA, 11.9% ABO). The development of antibodies seemed to play a subordinate role. As an examination for antibodies was performed only in case of clinical suspicion, but not systematically in all patients with unsatisfactory effect, this might underestimate the real number. Clinical testing of BoNT effectiveness using an EDB/frontalis test was executed only rarely. On the other hand, the categorization as treatment failure (and especially as primary or secondary) was retrospectively based on patients' statements and also included partial treatment failure. The numbers for primary or secondary treatment failure might not only include the development of clinically significant antibodies, but also the complexity of dystonic patterns or unrealistic patient expectations.

The rate of adverse events was comparably low in both groups [28]. Most frequently well-known effects such as dysphagia, muscle weakness and pain were reported. No severe adverse event leading to hospitalization or implantation of a feeding tube occurred in relation with BoNT-A. The frequency of the side effects was numerically higher in the ABO group, although no statistical comparison was performed. Side effects were most frequently reported during one's first year of treatment, though the mean dose was lower at that time. This might be partly explained by a changing reporting behavior after some treatment cycles, as some patients seem to be more introspective on therapy start after having received detailed information about possible side effects. Furthermore, the physician usually adapted the injection scheme after the occurrence of side effects. Ten patients stopped the therapy because of side effects.

The mean dose, effect duration and rate of side effects were comparable in patients with acquired dystonia and in patients with non-acquired dystonia, especially acknowledging the different group sizes. The descriptively lower satisfaction with the treatment effect by patients with acquired dystonia might result from psychiatric comorbidity in the

case of patients with neuroleptics-induced dystonia or from a sometimes more complex pattern of dystonia.

As a limitation of our retrospective study, the treatment effect has not been systematically quantified using an obligatory score by the treating physician. Though our documentation charts include the Tsui score [29], it had not been evaluated at each treatment cycle over the years. Therefore, to avoid a relevant bias due to missing data, we excluded the score from the analysis. Furthermore, the patients usually returned to us only for the reinjections, but not at the time of maximal effect. Considering this, the treatment effect was only evaluated by the patients' judgement on effect intensity and duration and by indirect parameters such as treatment adherence and dose stability. To avoid an over-interpretation of the data, we classified the patients' statements in only two categories without more precise graduation. Furthermore, we opted against statistical tests to compare ONA and ABO acknowledging the difficulty to adequately account for repeated observations in single subjects and possible temporal dependencies within in each subject. In line with the increasing focus on patient-centered parameters as quality of life and treatment satisfaction [30] on the one hand and the low practicability of complex scores as the TWSTRS score in daily routine [31] on the other hand, we believe that our focus on patients' treatment satisfaction ("good" in 86% of all treatment sessions) over our long observation period with frequent change of physicians is justified. Additionally, the Tsui score has been reported to often differ from the results of patients' subjective assessments [32].

In spite of these limitations, our results allow to assure patients that most other patients experience a satisfactory relieve of symptoms after the vast majority of treatments. Furthermore, it allows to give realistic numbers about the frequency of side effects. It allows to tell patients that although it is likely to suffer from a side effect at some point, most patients choose to stay in therapy. Therefore, we believe, our data—gathered during usual clinical practice—provide a solid base for patient counseling.

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Compliance with ethical standards

Conflicts of interest A Jochim has received travel grants from Ipsen Pharma GmbH, Merz Pharmaceuticals GmbH, Pharm-Allergan GmbH, Boston Scientific, Bayer Health and Universitätsklinikum Würzburg as well as speaker honoraria from Pharm-Allergan GmbH. T. Meindl has received travel grants from Ipsen Pharma GmbH, Merz Pharmaceuticals GmbH, Pharm-Allergan GmbH and Boston Scientific Medizintechnik. GmbH. T. Mantel has received travel grants from Bayer Vital GmbH. S. Zwirner has no conflicts of interest. M. Zech is supported by an internal research program at Helmholtz Center Munich, Germany ("Physician Scientists for Groundbreaking Projects"), has received travel expenses from Pharm-Allergan GmbH, and has received speaker honoraria from Bayer Vital GmbH. F. Castrop has no conflicts of interest. B. Haslinger has received research support from the German Research Foundation (DFG), Pharm-Allergan GmbH and Ipsen Pharma GmbH, has received speaker honoraria from Pharm-Allergan GmbH and Bayer Health Care Pharmaceuticals and has received travel grants from Ipsen Pharma GmbH.

Ethical approval The study has been approved by the local ethics review board. All patients whose data were not only acquired retrospectively, but also recorded prospectively, gave their written informed consent before entering the prospective phase of the study.

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