BMJ open

Factors influencing response to Botulinum toxin type A in patients with idiopathic cervical dystonia: Results from an international, observational study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-000881
Article Type:	Research
Date Submitted by the Author:	16-Jan-2012
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Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology
Keywords:	Neuromuscular disease < NEUROLOGY, Adult neurology < NEUROLOGY, Neurological pain < NEUROLOGY

Article type: Full Paper

PROPOSED TITLE: Factors influencing response to Botulinum toxin type A in patients with idiopathic cervical dystonia: Results from an international, observational study

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Key words: idiopathic cervical dystonia, botulinum toxin

Previous publications:

1. Poster presentation, “An International, Observational Study To Define Factors Influencing Response to Botulinum Toxin Type A (BoNT-A) in Subjects with Idiopathic Cervical Dystonia: Methodology and Baseline Clinical Data” at the 63rd Annual Meeting of the American Academy of Neurology, Honolulu, Hawaii, 9–16 April 2011. Abstract number P04.224.
2. Poster presentation, “An international, observational study to define in real life practice response to Botulinum toxin type A (BoNT-A) injection in subjects with idiopathic cervical dystonia” at The MDS 15th International Congress of Parkinson's Disease and Movement Disorders, Toronto, ON, Canada, 5–9 June 2011. Abstract number 662.
3. Poster presentation, “An international, observational study to identify in real life practice prognostic factors for response to Botulinum toxin type A injection in subjects with cervical dystonia” at the 15th Congress of the European Federation of Neurological Societies, Budapest, Hungary, 10–13 September 2011. Abstract number P1497.
4. Poster presentation, “An international, observational study to define in real life practice response to Botulinum toxin type A (BoNT-A) injection in subjects with idiopathic cervical dystonia” at the 7th International Conference on Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins – Toxins 2011, Santa Fe, USA, 2–5 October 2011.

Word count (abstract)/limit: 274/300 words
Word count (text)/limit: 3138/4000 words exclusive of title page, abstract, figures/tables, and references
Figures/tables/limit: 5/5 figures and/or tables
References/limit: 18/40

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ABSTRACT:

Objectives: Real-life data on response to Botulinum toxin A (BoNT-A) in cervical dystonia (CD) are sparse. An expert group of neurologists was convened with the overall aim to develop a definition of treatment response, which could be applied in a non-interventional study of BoNT-A-treated subjects with CD.

Design: International, multicentre, prospective, observational study of a single injection cycle of BoNT-A as part of normal clinical practice.

Setting: 38 centres across Australia, Belgium, Czech Republic, France, Germany, The Netherlands, Portugal, Russia and the United Kingdom.

Participants: 404 adult subjects with idiopathic CD. Most subjects were female, aged 41–60 years, and had previously received BoNT-A.

Outcome measures: Response was assessed according to a multidimensional definition based on four criteria: magnitude of effect (≥25% improvement Toronto Western Spasmodic Torticollis Rating Scale), duration of effect (≥12-week interval between the BoNT-A injection day and subject-reported waning of treatment effect), tolerability (absence of severe related adverse event), and subject's positive clinical global improvement (CGI).

Results: High rates of response were observed for magnitude of effect (73.6%), tolerability (97.5%), and subject's CGI (69.8%). The subjective duration of effect criterion was achieved by 49.3% of subjects; 28.6% of subjects achieved the responder definition. Factors most strongly associated to response were age (<40 years; odds ratio 3.9, $p<0.05$) and absence of baseline head tremor (odds ratio 1.5; not significant).

Conclusions: Three of four criteria were met by most patients. The proposed multidimensional definition of response appears to be practical for routine practice. Unrealistically high patient expectation and subjectivity may influence the perception of a quick waning of effect, but highlights that this aspect may be a hurdle to response in some patients.

Clinical trials information: (NCT00833196; clinicaltrials.gov)

ARTICLE SUMMARY

Article focus:

- Development and application of a novel multimodal definition of treatment response in a non-interventional study of patients with cervical dystonia (CD) administered Botulinum toxin A (BoNT-A) in routine clinical practice.

Key messages:

- Magnitude of effect, subject satisfaction and safety profile are appropriate measures of BoNT-A response in patients with CD.
- A multidimensional definition of response enables comprehensive evaluation of treatment response that is not achievable with a single measurement criterion.

Strengths and limitations of this study:

- This is a large-scale study of CD patient demographics and BoNT-A response in a real-life clinical setting.
- The subjective nature of self-reported waning of treatment effect is potentially vulnerable to bias as a result of high patient expectation, which constrains its use as part of the challenging multidimensional definition of response.

INTRODUCTION

Cervical dystonia (CD) is the most common of the focal dystonias,[1] with a prevalence ranging from 57 per million of the population of some European countries [2] to 89 per million in parts of the US (Rochester, Minnesota).[3] Any muscle in the neck may be abnormally contracted in CD. Sets of contracted muscles can be found in isolation, but are most commonly found in combination.[4] The majority of cases (~66%) present with rotational torticollis and laterocollis.[5] Co-morbidity with other movement disorders is common; therefore, classification of CD is based on the primary (idiopathic) or secondary aetiology.

Botulinum toxin A (BoNT-A) is a neurotoxin that is isolated and purified from *Clostridium botulinum* type A bacteria and has gained increasing acceptance as a first-line treatment option for CD. There is a substantial body of evidence from clinical studies to support the use of BoNT-A in patients with CD.[6-8] There are currently three major commercially available preparations of Type A toxins: abobotulinumtoxinA (Dysport®, Ipsen), onabotulinumtoxinA (Botox®, Allergan Incorporated) and incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmBH), which differ in their potency; thus, the units of each preparation are not directly interchangeable.

Although the efficacy and safety of BoNT-A is widely accepted according to robust and well-designed clinical trials; these studies assessed efficacy using mainly Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) or Tsui scale in highly selected patients, which may not relate to real-life practice with individualised patients. Furthermore, the administration of BoNT-A in practice does not reflect the standardised methods adopted in clinical studies because injection schemes are individually determined by the physician. Moreover, BoNT-A administration protocols for CD are not standardised to the subtypes of the condition (i.e. predominant and secondary components for head and neck deviations).

In clinical practice, assessment of BoNT-A effectiveness is multidimensional and cannot be limited to TWSTRS or Tsui scale only, but data on efficacy and safety of BoNT-A in real-world settings are lacking. There is, therefore, a clinical need to pragmatically describe the management of CD subtypes innovatively, taking into account several dimensions of interest for physicians, such as patient's satisfaction, and to establish a robust definition of response to BoNT-A treatment in the real-life management of patients with CD. A meeting of experienced neurologists from France, Germany, Italy, Russia, Spain, Thailand and the United Kingdom was convened in 2008, with a view to reaching a consensus on a definition of treatment response, a definition currently lacking in the clinical management of patients with CD receiving BoNT-A. The expert group identified the most relevant predominant and secondary components for head and neck deviations and concurred in proposing a new multidimensional definition of response, which was based on combined aspects of efficacy and tolerability and assessment of global improvement. We present,

herein, findings from the application of this novel definition of treatment response in a non-interventional study of subjects with CD who were administered BoNT-A. In this study, the primary objective was to estimate the responder rate following one BoNT-A injection cycle administered via routine practice.

SUBJECTS AND METHODS

Study design

This was an international, multicentre, observational, prospective, longitudinal study. Informed consent was obtained prior to subject enrolment and prior to any data collection. Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval in each country was obtained prior to study initiation.

Study population

This study enrolled subjects ≥18 years old, suffering from idiopathic CD with a TWSTRS severity score ≥15,[9] and a ≥12-week interval between the last injection (BoNT-A or BoNT-B) and the first study visit.

Subjects with secondary CD were excluded from the study, as were subjects with contraindications of BoNT-A treatment.

Study treatment

The decision to prescribe a BoNT-A preparation was taken prior to, and independently from, the decision to enrol the subject in the study. In order to avoid bias in the recruitment of subjects, physicians were not allowed to choose their subjects, but were asked to include consecutive subjects during BoNT-A consultations.

The prescribing of BoNT-A was made in accordance with routine clinical practice and investigators were free to choose: the targeted muscles from the clinically indicated neck muscles; BoNT-A preparation; and injected dose number of points and volume per point. Subjects received a single injection cycle as part of normal clinical practice. Concomitant therapy was permitted throughout the study.

Study assessments

Subjects were assessed during their usual centre visits at the inclusion visit (Visit 1; week 0); follow-up visit (Visit 2; 3–6 weeks after injection); and end-of-study visit (Visit 3; 12–16 weeks after injection). Efficacy assessments encompassed clinical assessment; assessment of CD using the TWSTRS total score (recorded at all visits);[10] assessment of tremor using the Tsui Tremor subscale (recorded at all visits);[11] assessment of Clinical Global Improvement (CGI) by both Investigator and subject (recorded at Visit 2); and CD Impact Profile-58 (CDIP-58) (recorded at Visits 1 and 2).[12] The CDIP-58 comprises a 16-item health-related quality of life (HRQoL) questionnaire encompassing domains relating to head and neck symptoms experienced by the subject, impact on usual daily activities, physical activities, sleep, social activities, and emotions/psychosocial functioning. Scores for items within domains were

summarised into eight subscale scores, each ranging from 0 to 100 (higher scores indicate worse health).

The primary endpoint of this study was the percentage of responders after one BoNT-A injection cycle. Response was defined using the ambitious hypothesis for a multidimensional definition of response developed by experienced neurologists, whereby subjects were classified as a responder if they met all of the following criteria: 1) magnitude of effect: ≥25% improvement on TWSTRS severity scale at Visit 2 (peak effect) or Visit 3 (if Visit 2 was not performed), compared with Visit 1, as reported by Truong et al. in 2005;[9] 2) duration of effect: ≥12-week interval between the BoNT-A study injection day and the day the subject reports a clinically relevant waning of treatment effect, justifying a re-injection cycle as reported by Ranoux et al. in 2002;[13] 3) good tolerance: no treatment-related severe adverse event (AE) reported during the study; and 4) Subject-rated CGI score at Visit 2 and Visit 3 equal to either +2 (much improved) or +3 (very much improved).

Secondary efficacy outcomes included improvements in TWSTRS total and Severity, Disability and Pain subscale scores, tremor (as measured by TSUI score) and CDIP-58.

Only AEs considered by the Investigator to be related to study drug were collected during this study, which is in line with current clinical practice. Investigators were asked to report, to the safety department of the BoNT-A manufacturer, any adverse drug reactions using the usual process for such reactions. More specifically on Visits 2 and 3, investigators were also requested to document the occurrence and intensity (severe or not) of dysphonia, dysphagia, neck muscle weakness and other.

Study size

The sample size was determined based on both the primary and exploratory objectives. Considering an anticipated rate of responder of 50%, using an estimate for this proportion with a precision of 5%, the required sample size was determined to be 385 subjects (assuming a two-sided 95% confidence interval [CI]). When considering the objective related to the detection of prognostic factors (assuming Alpha=5%, Power=80%), in order to ensure the ability to detect odds ratio ≥2 and a probability to be exposed to any given level of a prognostic factor larger or equal to 1/3 (=imbalance), the required sample size is 366 subjects. Thus in order to ensure 385 evaluable subjects, 400 subjects were included in this study.

Statistical analyses

The safety population consisted of all subjects who received one BoNT-A injection, whereas the efficacy population comprised all subjects in the treated population for whom there were data for each of the four underlying variables for response. The responder analysis was

performed using the efficacy population and all secondary endpoints were assessed using the safety population.

The primary endpoint was summarised overall, and by each of the four criteria, as the percentage of responders as a point estimate and its associated 95% CI. Responder subgroup analyses were also performed to investigate response based on the following criteria: predominant component of head/neck rotation; BoNT-A preparations; duration of CD; previous BoNT-A use; dystonia localisation (head/neck, trunk, limbs); presence of tremor based on the TSUI scale; use of electromyography (EMG); and use of concomitant therapies at baseline.

As an exploratory analysis, a stepwise multivariate logistic regression analysis was performed on the efficacy population to assess prognostic factors for response using subgroup variables, as well as additional demographic and disease characteristics variables. Odds ratios (OR) with 95% CI estimated by the logistic model were calculated using the primary criteria; a lower 95% CI bound >1 indicated a significantly increased chance of being a responder.

No estimations were made for missing data and there was no controlling for confounding factors.

RESULTS

Subject population

Between 19 February 2009 and 12 February 2010, 404 subjects from 38 centres in 9 countries (Australia, Belgium, Czech Republic, France, Germany, The Netherlands, Portugal, Russia and the United Kingdom) were enrolled and followed in this study. A total of 379 subjects (93.8%) completed the study. The most common reason for not completing the study was loss to follow-up (3.2%; n=13); no subjects discontinued due to lack of efficacy.

The safety population included all subjects treated with BoNT-A (n=404), whereas the efficacy population included all subjects treated with BoNT-A for whom data were available for each of the four criteria for the primary endpoint (n=367).

Baseline demographic and disease characteristics are shown in Table 1. The majority of subjects were female (64.9%), aged 41–60 years (52.5%), and had suffered from CD for >1 year (90.9%). Nearly all of the subjects had sporadic CD (94.8%), and focal dystonia predominated (91.6%). In the few cases of segmental/multifocal dystonias, the upper limb was the most frequently impaired segment. The most common predominant component of CD was rotation (72.8%), followed by laterocollis (14.1%). The majority of subjects had secondary components (83.9%).

Table 1: Subject demographics and CD characteristics (safety population)

Demographic/characteristic		Total, n=404
Gender, n (%)	Male	142 (35.1)
	Female	262 (64.9)
Age (years), n (%)	18 to 30	18 (4.5)
	31 to 40	52 (12.9)
	41 to 50	105 (26.0)
	51 to 60	107 (26.5)
	61 to 70	81 (20.0)
	>70	41 (10.1)
Body weight (kg), mean (SD)		72.8 (14.9)
Duration of cervical dystonia, n (%)	<6 months	10 (2.5)
	6 months to <1 year	27 (6.7)
	1 to 5 years	140 (34.7)
	6 to 10 years	89 (22.0)
	11 to 20 years	84 (20.8)
	>20 years	54 (13.4)
Type of cervical dystonia, n (%)	Sporadic	383 (94.8)
	Familial	21 (5.2)
Location type, n (%)	Focal	370 (91.6)
	Segmental	20 (5.0)
	Multi-focal	9 (2.2)

	Generalised	5 (1.2)
Localisation, n (%)	Head/neck	404 (100.0)
	Trunk	13 (3.2)
	Upper limb	29 (7.2)
	Lower limb	6 (1.5)
Predominant component, n (%)	Rotation	294 (72.8)
	Laterocollis	57 (14.1)
	Tremor	20 (5.0)
	Retrocollis	12 (3.0)
	Shoulder elevation	8 (2.0)
	Anterocollis	4 (1.0)
	Jerk	4 (1.0)
	Lateral shift of column	3 (0.7)
	Sagittal shift of column	2 (0.5)
Secondary components present, n (%)	Yes	339 (83.9)
Most frequent combinations of predominant and secondary components, n (%)	Rotation and laterocollis	161 (39.9)
	Rotation and shoulder elevation	143 (35.4)
	Rotation and tremor	73 (18.1)
TWSTRS score at baseline, mean ± SD	Severity subscale Disability subscale Pain subscale Total score	19.5 ± 3.8 10.6 ± 5.9 6.6 ± 4.9 36.8 ± 10.7
Baseline tremor present	n (%)	191 (47.3)
CDIP-58 subscales scores[a], mean ± SD	Head and neck symptoms Pain and discomfort Upper limb activities Walking Sleep Annoyance Mood Psychosocial	50.6 ± 25.2 31.8 ± 27.8 26.1 ± 24.6 22.4 ± 26.7 23.0 ± 31.0 26.4 ± 27.7 21.6 ± 25.9 30.7 ± 28.2

[a]CDIP-58 n=99 (questionnaire in English, thus completed by English speaking patients only).

Treatment history

Most subjects had previously received a BoNT-A injection (84.9%). Of the safety population, more than half of subjects (n=215; 53.2%) had previously received benzodiazepines for the treatment of CD and approximately one-third (29.7%) continued to receive these agents after BoNT-A treatment. Prior physical therapy was reported in 49.8% of subjects, but only 14.6% of subjects were receiving physical therapy at the inclusion visit. Analgesics had been previously taken by 40.8% of subjects, with 18.3% of subjects receiving analgesics at the inclusion visit.

Injection schemes

Physicians prescribed three BoNT-A preparations: Dysport (n=279, 69%), Botox (n=113, 28%) and Xeomin (n=12, 3%), independently from study enrolment, as per local clinical practice at the center. Subjects received Dysport and Botox at median doses of 500 and 160 units, respectively. Overall, the median number of injected muscles was four; of which, the most frequently injected muscles in both the Dysport and Botox groups were the splenius capitis, sternocleidomastoid and trapezius. The number of patients treated with Xeomin was too small for a meaningful analysis. Investigators used EMG during administration of at least one muscle in 185 subjects (46.0%).

Efficacy

Responder analysis

The percentage of subjects meeting the response criteria, as well as each of the individual response criteria, is shown in Figure 1. Three criteria out of four were achieved in the majority of patients, as shown by 97.5%, 73.6% and 69.8% of subjects achieving criterion of magnitude of effect, tolerance (absence of severe related AEs) and subject's CGI, respectively. A total of 49.3% of subjects achieved response based on the duration of effect criterion (≥12 weeks between inclusion and subject-rated waning of treatment effect). Overall, 28.6% (95% CI: 24.0% to 33.5%) of subjects were classified as responders to treatment. Evaluation of response by TWSTRS, tolerance and CGI improvement alone (i.e. exclusion of duration of effect) established 58.3% (95% CI: 53.1% to 63.4%) of subjects as responders.

Responder subgroup analysis

Analysis of the response criteria by subgroup is shown in Figure 2 and showed that there were variations in response, albeit these results were not statistically significant. Data revealed that more subjects responded among subgroups presenting with laterocollis (41.7% versus 26.7% with rotation), without baseline tremor (33.2% versus 23.7% with tremor), and

those not receiving concomitant medication at baseline (35.1% versus 22.8% receiving baseline concomitant medications).

Prognostic factors associated with response

The multivariate logistic regression showed that the most strongly associated factors to response were age (<40 years) and absence of baseline head tremor: corresponding ORs were 3.9 ($p< 0.05$) for age and 1.5 (not significant) for absence of tremor. Additional trends with a lower magnitude of association were observed (data not shown).

Secondary efficacy outcomes

Secondary efficacy outcomes are shown in Table 2. Subjects reported a notable improvement in TWSTRS total score and subscale scores over the course of treatment, as indicated by the percentage change in scores at each visit. Sixty-six of the 181 subjects (36.5%) with baseline tremor no longer presented with tremor at Visit 2. HRQoL improved following BoNT-A treatment, as demonstrated by decreases in all eight subscores of the CDIP-58 at Visit 2.

Table 2. Efficacy outcomes

	Visit 2	Visit 3
Percentage change in TWSTRS Score, mean ± SD	(n=374)	(n=380)
Severity subscore	–40.8 ± 25.1	–16.5 ± 22.3
Disability subscore	–36.3 ± 49.8	–6.6 ± 90.2
Pain subscore	–35.8 ± 49.9	–7.6 ± 72.6
Total score	–39.6 ± 26.6	–15.4 ± 27.0
Tremor	(n=375)	(n=380)
Subjects with improvement in tremor[a] with treatment, n (%)	66/181[b] (36.5)	41/178[a] (23.0)
CDIP-58 subscales scores, mean ± SD	(n=93[c])	–
Head and neck symptoms	26.1 ± 21.9	–
Pain and discomfort	20.5 ± 23.5	–
Upper limb activities	16.3 ± 19.9	–
Walking	15.3 ± 21.5	–
Sleep	12.3 ± 20.0	–
Annoyance	15.6 ± 23.9	–
Mood	13.9 ± 20.5	–
Psychosocial functioning	19.2 ± 23.6	–

[a]Improvement defined by presence of tremor at baseline and absence of tremor at subsequent visits.

[b]Subjects with data available at this timepoint and with tremor present at baseline.

[c]Questionnaire in English, thus completed by English speaking patients only.

Safety and tolerability

A total of 88 treatment-related AEs were reported during the study. Overall, 68 subjects (16.8%) experienced at least one treatment-related AE. Of the observed AEs, dysphagia was the most commonly reported (9.2%). Overall, ten treatment-related AEs were considered to be severe, with neck muscle weakness (n=4) being observed as the most common AE at this grade of severity. The incidence of AEs (severe and not severe) and dysphagia did not statistically differ between BoNT-A preparations (Figure 3).

DISCUSSION

In this non-interventional study of subjects with CD in routine practice, the majority of subjects were middle-aged women. These demographic data were in accordance with a typical population of subjects with CD.[14] TWSTRS and CDIP-58 scores at baseline reflected a population with moderate to severe CD severity.

Real-life data on response to BoNT-A in CD are sparse. Therefore, the primary objective of this study was to estimate the rate of response following one BoNT-A injection cycle in real-life practice using a challenging multidimensional definition developed by an expert group of neurologists. To our knowledge, this is the first such non-interventional study to apply a consensus-based multimodal definition of response to a large real-world population of patients with CD treated with BoNT-A. Notably, this ambitious definition for response was achieved by almost one-third (approximately 30%) of the 404 subjects who participated in this study. Although the magnitude of effect and subject satisfaction were both high and the number of treatment-related severe AEs was very low, the number of subjects with a duration of effect ≥12 weeks was relatively low. These novel findings indicate that measurements for the magnitude of effect, subject satisfaction and safety profile according to routine practice demonstrate good clinical response to BoNT-A in subjects suffering from CD. However, duration of effect such as defined in the study may require further confirmation due to its subjective nature. Waning of effect is a gradual process and therefore assessment for duration of effect based on serial subject's CGI measurements (rather than depending on the patient reporting on waning of effect on a single specific date) may have been more appropriate. Regardless of these considerations, unrealistically high patient expectation and subjectivity may influence the perception of quick waning of effect. This highlights that, for some patients, this aspect is seen as a hurdle to response.

The subgroup analyses suggest that laterocollis as a predominant component, the absence of baseline tremor and absence of concomitant medication are factors that may be associated with higher response rates. Even if these data were not statistically significant, they provide a good starting point for further evaluation. In particular, it would be interesting to establish whether the use of concomitant medication at baseline reflects a greater disease severity (as assessed with TWSTRS scores) or more co-morbidities associated with CD (e.g. anxiety, depression) that could interfere with the therapeutic effect of BoNT-A. With relevance to the former, data from this study suggest that the duration of CD (≤10 years versus >10 years) did not markedly influence the distribution of concomitant therapies (data not shown).

Efficacy findings confirm the value of BoNT-A as a treatment for CD symptoms. Notable improvements in mean TWSTRS scores were observed, as was improvement in tremor. It is recognised that HRQoL is compromised in CD, especially among women.[15] In

this analysis of a largely female population, the decrease in subscores of the CDIP-58 (a more sensitive measure of clinical change than other frequently used HRQoL instruments[12] is consistent with previous reports in confirming the positive impact of BoNT-A on HRQoL when administered as a therapy for CD.[15, 16]

BoNT-A was generally well tolerated in this study, with few reported severe AEs. In general, treatment-emergent side effects were consistent with the known safety profile of this treatment.[17] As observed in previous reports, the most common side effect of BoNT-A treatment was dysphagia.[17, 18] Overall, this study highlights that no new safety concerns were raised with BoNT-A when used in routine clinical practice. For any given treatment, an acceptable level of tolerance is required to ensure continued treatment and subject compliance; hence the inclusion of tolerance as a response criterion. In total, 97.5% of subjects met the response criterion of no severe treatment-related AEs. It may be speculated that the presence of treatment-emergent side effects such as dysphagia could exert a negative impact on objective and subjective assessments of symptom improvement and ultimately response, but observed response rates of 73.6% (magnitude of effect) and 69.8% (subject's CGI) in this study would suggest otherwise.

Inherent to studies of this design, the non-interventional nature of the study means that confirmatory conclusions cannot be drawn. Moreover, the *a priori* defined duration of effect criteria was based on subject assessment of the waning of treatment effect. Thus, the subjective nature of this assessment has potential for bias resulting from patients' unrealistically high expectations from treatment; a hypothesis supported by the observation of maintained improvements in TWSTRS scores even at Visit 3.

CONCLUSIONS

This study reveals the CD subject demographics and BoNT-A response in a real-life clinical setting. Using a novel multimodal definition of response, this large-scale study showed that the magnitude of effect, subject satisfaction and safety profile were well met and it was also felt that these were appropriate measures to assess BoNT-A response in CD subjects. The date of waning of treatment effect, as perceived by the subject on a specific day, is probably too subjective to be clinically appropriate enough to be used as part of this challenging multidimensional response definition, serial subject's CGI may be a better measure to give a more appropriate indication of duration of action. A multidimensional definition of response does, however, allow a comprehensive assessment of the patient's response to treatment, which cannot be achieved by using a single criterion. This study also indicates possible predictive factors for BoNT-A in subjects with CD, but further research is required to confirm these in the prognosis of CD.

Acknowledgments: The authors would like to acknowledge the editorial assistance of Ogilvy Healthworld. Funding was provided by Ipsen.

The authors would also like to thank members of the INTEREST IN CD study group, who were:
Australia: Dr A Hughes, Dr K Kotschet, Dr D Williams, Dr V Fung; Belgium: Dr M van Zandijcke, Dr P Santens, Dr W van Landegem, Dr V Delvaux; Czech Rep: Dr E Ehler, Dr R Jech, Dr P Otruba, Dr M Bareš; France: Dr M Simonetta-Moreau, Dr S Soulayrol, Dr P M Burbaud, Dr A Kreisler, Dr C Vial, Dr M Borg, Dr S Sangla, Dr N Patte-Karsenti; Germany: Dr E Fleischer, Dr M Müngersdorf, Dr I Weimar, Dr R Pfister, Dr B Mohammadi, Dr I Nastos; Netherlands: Dr Laboyrie, Dr Douma; Portugal: Dr M J Rosas, Dr J Ferreira, Dr M Castelo Branco; Russia: Dr S Timerbaeva, Dr D Khasanova, Dr L Korenko, Dr G Belskaya;
UK: Dr P Moore, Dr M Kellet, Dr P Misra, Dr T Harrower.

Competing interests

Vijay P. Misra
Consultancies: *Ad hoc* consultant to Ipsen Pharma and Syntaxin Ltd..
Advisory Boards: Attended Ipsen Pharma Medical Advisory Boards.
Contracts: Contracts with Ipsen Pharma and Syntaxin Ltd. related to *ad hoc* Consultancies/Advisory boards.

Edvard Ehler
Grants: IGA Ministry of Health, Czech Republic.

Benjamin Zakine and Pascal Maisonobe
Employment: Ipsen.

Marion Simonetta-Moreau
Consultancies: Ipsen.
Employment: Hôpitaux de Toulouse and Paul Sabatier University.

Funding statement
This study was supported by Ipsen Pharma; employees (Benjamin Zakine and Pascal Maisonobe) of whom were involved in the design of the study and the subsequent preparation of this manuscript (writing and review).

Contributor statement

Vijay P. Misra was involved in the concept and design, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript review and critique, and final approval of manuscript.

Edvard Ehler was involved in the provision of study materials or patients, collection and assembly of data, manuscript review and critique, and final approval of manuscript.

Benjamin Zakine was involved in the concept and design, data analysis and interpretation, manuscript writing, manuscript review and critique, and final approval of manuscript.

Pascal Maisonobe was involved in the concept and design, data analysis and interpretation, manuscript writing, manuscript review and critique, and final approval of manuscript.

Marion Simonetta-Moreau was involved in the concept and design, provision of study materials or patients, manuscript review and critique, and final approval of manuscript.

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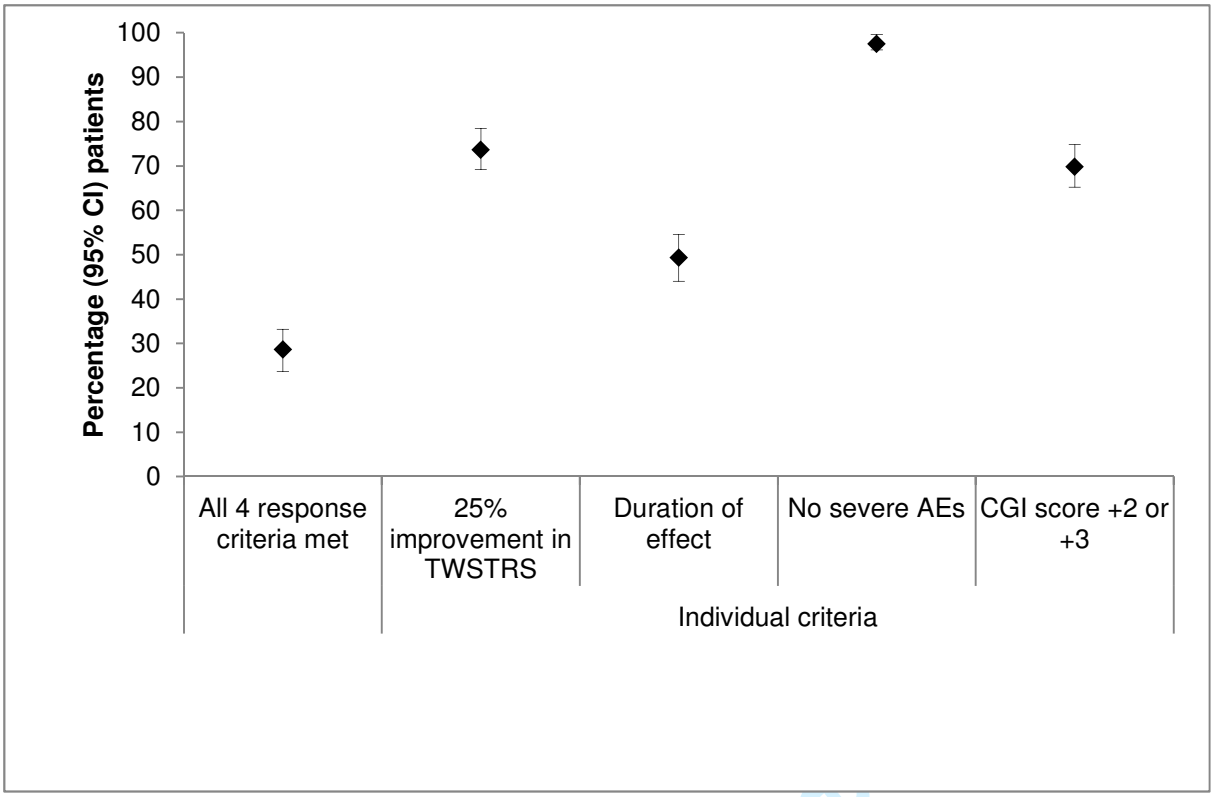
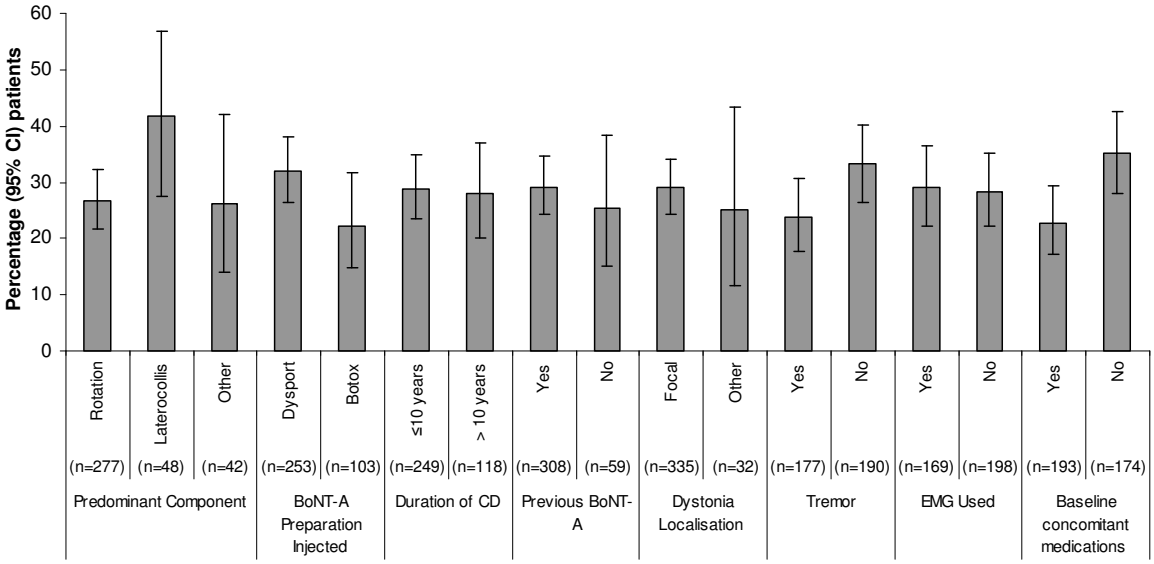
Figures

Figure 1: Responder analysis



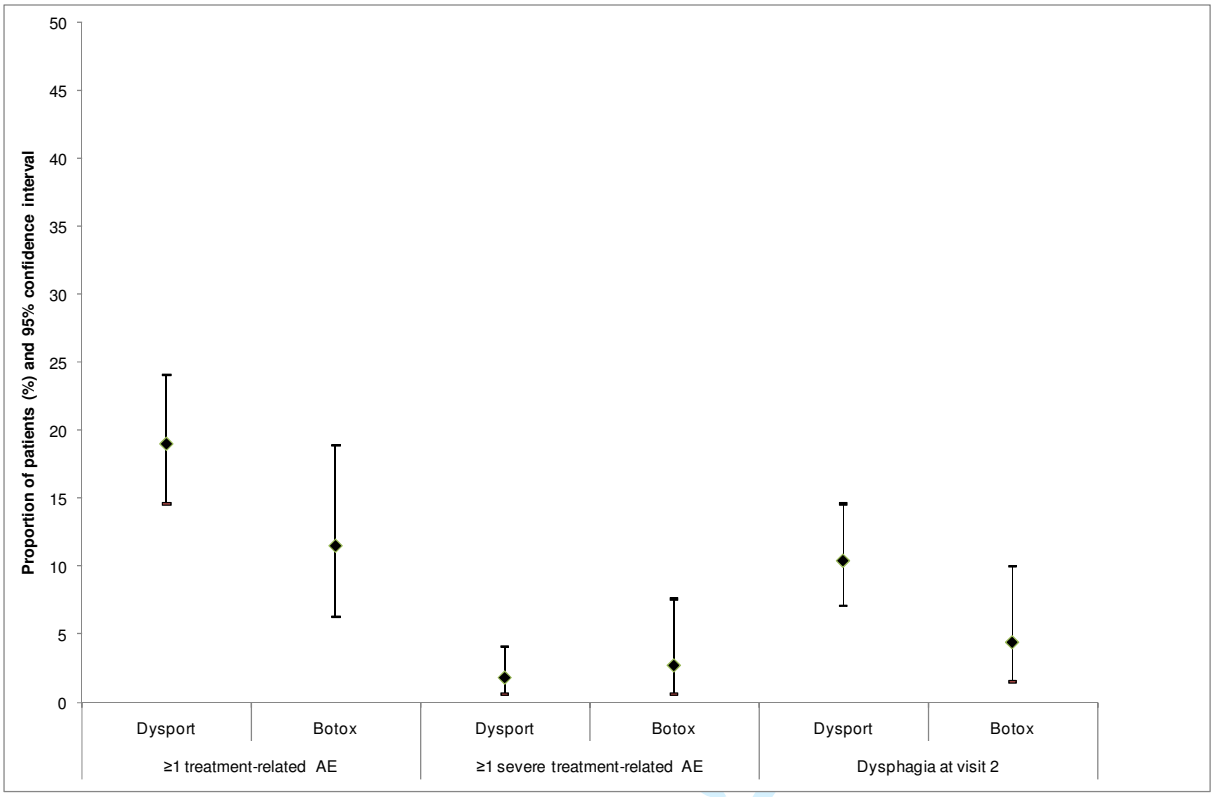
CI=confidence interval; TWSTRS=Toronto Western Spasmodic Torticollis Rating Scale; AEs=adverse events; CGI=clinical global improvement.

Figure 2: Subgroup analyses of responders (efficacy population)

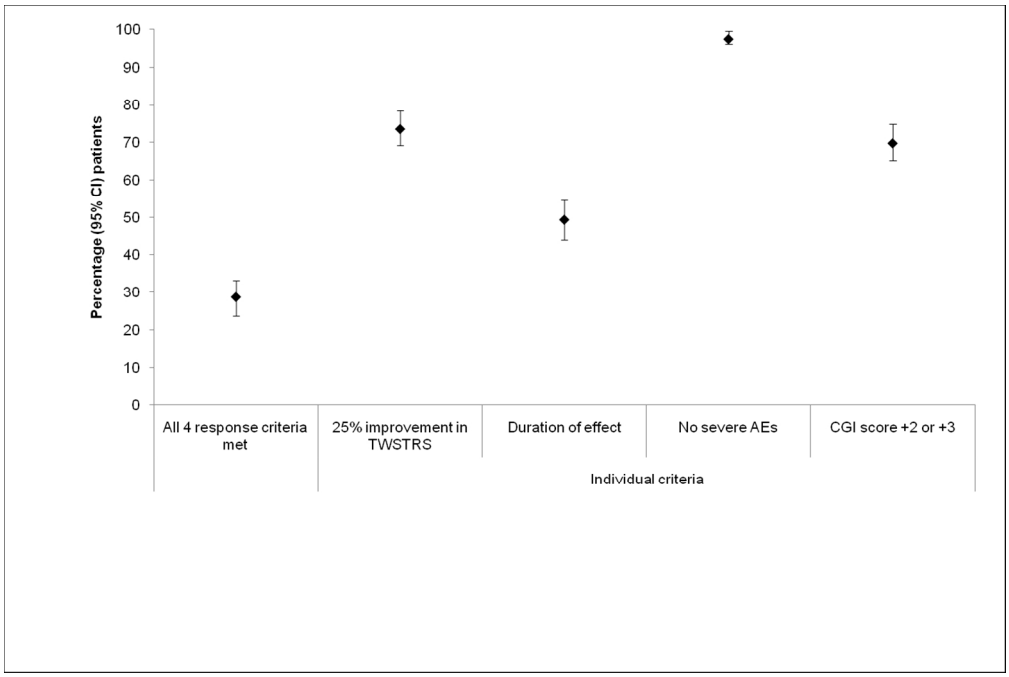


CI=confidence interval; CD=cervical dystonia; EMG = Electromyography; BoNT-A=Botulinum toxin A.

Figure 3: Occurrence of adverse events with frequently used BoNT-A preparation



BoNT-A=Botulinum toxin A; AE=adverse event.



Responder analysis
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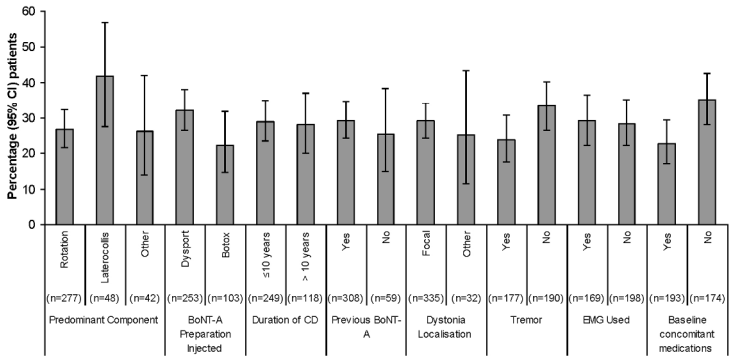
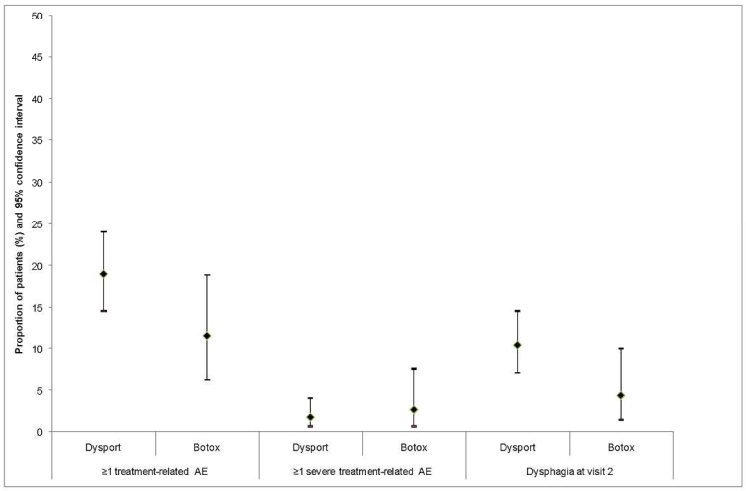


Subgroup analyses of responders (efficacy population)
297x210mm (200 x 200 DPI)



Occurrence of adverse events with frequently used BoNT-A preparation
297x210mm (200 x 200 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract - yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found- yes
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported- yes
Objectives	3	State specific objectives, including any prespecified hypotheses - yes
Methods		
Study design	4	Present key elements of study design early in the paper- yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection- yes
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up- yes
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable –these data are not relevant
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - NA
Bias	9	Describe any efforts to address potential sources of bias - yes
Study size	10	Explain how the study size was arrived at – was there a sample size calculation? Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding? No control for confounding factors
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed Missing data handling was addressed in the SAP (no estimation was made)
		(*d*) If applicable, explain how loss to follow-up was addressed - NA
		(*e*) Describe any sensitivity analyses - NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed -yes
		(b) Give reasons for non-participation at each stage - NA
		(c) Consider use of a flow diagram - NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders - yes
		(b) Indicate number of participants with missing data for each variable of interest - yes
		(c) Summarise follow-up time (eg, average and total amount) -NA
Outcome data	15*	Report numbers of outcome events or summary measures over time - YES

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - Not relevant
		(*b*) Report category boundaries when continuous variables were categorized- Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period- Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses- Not relevant
Discussion		
Key results	18	Summarise key results with reference to study objectives - yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias - yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - yes
Generalisability	21	Discuss the generalisability (external validity) of the study results -yes
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - yes

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Factors influencing response to Botulinum toxin type A in patients with idiopathic cervical dystonia: Results from an international, observational study

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-000881.R1
Article Type:	Research
Date Submitted by the Author:	10-Apr-2012
Complete List of Authors:	Misra, Vijay; The National Hospital for Neurology & Neurosurgery, Ehler, Edvard; County Hospital Pardubice, Department of Neurology Zakine, Benjamin; Ipsen Pharma, Global medical Affairs Maisonobe, Pascal; Ipsen Pharma, Biostatistics & Data Management Simonetta-Moreau, Marion; IPôle Neurosciences, Hôpitaux de Toulouse, Pavillon Riser & INSERM U825, Pavillon Baudot Purpan Hospital, Department of Neurology
Primary Subject Heading:	Neurology
Secondary Subject Heading:	Neurology
Keywords:	Neuromuscular disease < NEUROLOGY, Adult neurology < NEUROLOGY, Neurological pain < NEUROLOGY

Article type: Full Paper

PROPOSED TITLE: Factors influencing response to Botulinum toxin type A in patients with idiopathic cervical dystonia: Results from an international, observational study

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Key words: idiopathic cervical dystonia, botulinum toxin

Previous publications:

1. Poster presentation, “An International, Observational Study To Define Factors Influencing Response to Botulinum Toxin Type A (BoNT-A) in Subjects with Idiopathic Cervical Dystonia: Methodology and Baseline Clinical Data” at the 63rd Annual Meeting of the American Academy of Neurology, Honolulu, Hawaii, 9–16 April 2011. Abstract number P04.224.
2. Poster presentation, “An international, observational study to define in real life practice response to Botulinum toxin type A (BoNT-A) injection in subjects with idiopathic cervical dystonia” at The MDS 15th International Congress of Parkinson's Disease and Movement Disorders, Toronto, ON, Canada, 5–9 June 2011. Abstract number 662.
3. Poster presentation, “An international, observational study to identify in real life practice prognostic factors for response to Botulinum toxin type A injection in subjects with cervical dystonia” at the 15th Congress of the European Federation of Neurological Societies, Budapest, Hungary, 10–13 September 2011. Abstract number P1497.
4. Poster presentation, “An international, observational study to define in real life practice response to Botulinum toxin type A (BoNT-A) injection in subjects with idiopathic cervical dystonia” at the 7th International Conference on Basic and Therapeutic Aspects of Botulinum and Tetanus Toxins – Toxins 2011, Santa Fe, USA, 2–5 October 2011.

Word count (abstract)/limit: 276/300 words
Word count (text)/limit: 3278/4000 words exclusive of title page, abstract, figures/tables, and references
Figures/tables/limit: 5/5 figures and/or tables
References/limit:20/40

Copyright statement

ABSTRACT:

Objectives: Real-life data on response to Botulinum toxin A (BoNT-A) in cervical dystonia (CD) are sparse. An expert group of neurologists was convened with the overall aim to develop a definition of treatment response, which could be applied in a non-interventional study of BoNT-A-treated subjects with CD.

*Design:*International, multicentre, prospective, observational study of a single injection cycle of BoNT-A as part of normal clinical practice.

Setting: 38 centres across Australia, Belgium, Czech Republic, France, Germany, The Netherlands, Portugal, Russia and the United Kingdom.

*Participants:*404 adult subjects with idiopathic CD.Most subjects were female, aged 41–60 years, and had previously received BoNT-A.

Outcome measures: Patients were classified as responders if they met all of the following four criteria: magnitude of effect (≥25% improvement Toronto Western Spasmodic Torticollis Rating Scale), duration of effect (≥12-week interval between the BoNT-A injection day and subject-reported waning of treatment effect), tolerability (absence of severe related adverse event), and subject's positive clinical global improvement (CGI).

Results: High rates of response were observed for magnitude of effect (73.6%), tolerability (97.5%), and subject's CGI (69.8%). The subjective duration of effect criterion was achieved by 49.3% of subjects; 28.6% of subjects achieved the responder definition. Factors most strongly associated to response were age (<40 years; odds ratio 3.9, p<0.05) and absence of baseline head tremor (odds ratio 1.5; not significant).

Conclusions: Three of four criteria were met by most patients. The proposed multidimensional definition of response appears to be practical for routine practice. Unrealistically high patient expectation and subjectivity may influence the perception of a quick waning of effect, but highlights that this aspect may be a hurdle to response in some patients.

Clinical trials information:(NCT00833196; clinicaltrials.gov)

ARTICLE SUMMARY

Article focus:

- Development and application of a novel multimodal definition of treatment response in a non-interventional study of patients with cervical dystonia (CD) administered Botulinum toxin A (BoNT-A) in routine clinical practice.

Key messages:

- Magnitude of effect, subject satisfaction and safety profile are appropriate measures of BoNT-A response in patients with CD.
- A multidimensional definition of response enables comprehensive evaluation of treatment response that is not achievable with a single measurement criterion.

Strengths and limitations of this study:

- This is a large-scale study of CD patient demographics and BoNT-A response in a real-life clinical setting.
- The subjective nature of self-reported waning of treatment effect is potentially vulnerable to bias as a result of high patient expectation, which constrains its use as part of the challenging multidimensional definition of response.

INTRODUCTION

Cervical dystonia (CD) is the most common of the focal dystonias,[1] with a prevalence of 89 per million in parts of the US (Rochester, Minnesota).[2] Any muscle in the neck may be abnormally contracted in CD. Sets of contracted muscles can be found in isolation, but are most commonly found in combination.[3] The majority of cases (~66%) present with rotational torticollis and laterocollis.[4] Classification of CD is based on the primary (idiopathic) or secondary aetiology (e.g., dystonia because of a brain tumour).[5]

Botulinum toxin A (BoNT-A) is a neurotoxin that is isolated and purified from *Clostridium botulinum* type A bacteria and has gained increasing acceptance as a first-line treatment option for CD.[6] There is a substantial body of evidence from clinical studies to support the use of BoNT-A in patients with CD.[5,7–9] There are currently three major commercially available preparations of Type A toxins: abobotulinumtoxinA (Dysport®, Ipsen), onabotulinumtoxinA (Botox®, Allergan Incorporated) and incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH), which differ in their potency; thus, the units of each preparation are not directly interchangeable.BoNT-B has also gained acceptance in the treatment of patients with CD resistant to treatment with BoNT-A.[10]

The administration of BoNT-A in practice does not reflect the standardised methods adopted in clinical studies because injection schemes are individually determined by the physician. Moreover, BoNT-A administration protocols for CD are not standardised to the subtypes of the condition (i.e. predominant and secondary components for head and neck deviations). Although the efficacy and safety of BoNT-A is widely accepted according to robust and well-designed clinical trials; these studies assessed efficacy using mainly Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) or Tsui scale in highly selected patients, which may not relate to real-life practice with individualised patients.

In clinical practice, assessment of BoNT-A effectiveness is multidimensional and cannot be limited to TWSTRS or Tsui scale only, but data on efficacy and safety of BoNT-A in real-world settings are lacking. There is, therefore, a clinical need to pragmatically describe the management of CD subtypes innovatively, taking into account several dimensions of interest for physicians, such as patient's satisfaction, and to establish a robust definition of response to BoNT-A treatment in the real-life management of patients with CD. A meeting of experienced neurologists from France, Germany, Italy, Russia, Spain, Thailand and the United Kingdom was convened in 2008, with a view to reaching a consensus on a definition of treatment response, a definition currently lacking in the clinical management of patients with CD receiving BoNT-A. The expert group identified the most relevant predominant and secondary components for head and neck deviations and concurred in proposing a new multidimensional definition of response, which was based on combined aspects of efficacy and tolerability and assessment of global improvement. We present,

herein, findings from the application of this novel definition of treatment response in a non-interventional study of subjects with CD who were administered BoNT-A. In this study, the primary objective was to estimate the responder rate following one BoNT-A injection cycle administered via routine practice. Prognostic factors for response were evaluated as an additional exploratory analysis.

SUBJECTS AND METHODS

Study design

This was an international, multicentre, observational, prospective, longitudinal study. Informed consent was obtained prior to subject enrolment and prior to any data collection. Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval in each country was obtained prior to study initiation.

Study population

This study enrolled subjects ≥18 years old, suffering from idiopathic CD with a TWSTRS severity score ≥15,[9] and a ≥12-week interval between the last injection (BoNT-A or BoNT-B) and the first study visit.

To create a homogeneous population for study, subjects with secondary CD were excluded from the study, as were subjects with contraindications of BoNT-A treatment.

Study treatment

The decision to prescribe a BoNT-A preparation was taken prior to, and independently from, the decision to enrol the subject in the study. In order to avoid bias in the recruitment of subjects, physicians were not allowed to choose their subjects, but were asked to include consecutive subjects during BoNT-A consultations.

The prescribing of BoNT-A was made in accordance with routine clinical practice and investigators were free to choose: the targeted muscles from the clinically indicated neck muscles; BoNT-A preparation; and injected dose number of points and volume per point. Subjects received a single injection cycle as part of normal clinical practice. Concomitant therapy was permitted throughout the study.

Study assessments

Subjects were assessed during their usual centre visits at the inclusion visit (Visit 1; week 0); follow-up visit (Visit 2; 3–6 weeks after injection); and end-of-study visit (Visit 3; 12–16 weeks after injection). Efficacy assessments encompassed clinical assessment; assessment of CD using the TWSTRS total score (recorded at all visits);[11] assessment of tremor using the Tsui Tremor subscale (recorded at all visits);[12] assessment of Clinical Global Improvement (CGI) by both Investigator and subject (recorded at Visit 2); and CD Impact Profile-58 (CDIP-58) (recorded at Visits 1 and 2).[13] The CDIP-58 comprises a 16-item health-related quality of life (HRQoL) questionnaire encompassing domains relating to head and neck symptoms experienced by the subject, impact on usual daily activities, physical activities, sleep, social activities, and emotions/psychosocial functioning. Scores for items within domains were

summarised into eight subscale scores, each ranging from 0 to 100 (higher scores indicate worse health).

The primary endpoint of this study was the percentage of responders after one BoNT-A injection cycle. Response was defined using the ambitious hypothesis for a multidimensional definition of response developed by experienced neurologists, whereby subjects were classified as a responder if they met all of the following criteria: 1) Magnitude of effect: ≥25% improvement on TWSTRS severity scale at Visit 2 (peak effect) or Visit 3 (if Visit 2 was not performed), compared with Visit 1, as reported by Truong et al. in 2005;[9] 2) Duration of effect: ≥12-week interval between the BoNT-A study injection day and the day the subject reports a clinically relevant waning of treatment effect, justifying a re-injection cycle as reported by Ranoux et al. in 2002;[14] 3) Good tolerance: no treatment-related severe adverse event (AE) reported during the study; and 4) Improvement in subject-rated CGI score at Visit 2 and Visit 3 (equal to either +2 [much improved] or +3 [very much improved]).

Secondary efficacy outcomes included improvements in TWSTRS total and Severity, Disability and Pain subscale scores, tremor (as measured by TSUI score) and CDIP-58.

Only AEs considered by the Investigator to be related to study drug were collected during this study, which is in line with current clinical practice. Investigators were asked to report, to the safety department of the BoNT-A manufacturer, any adverse drug reactions using the usual process for such reactions. More specifically on Visits 2 and 3, investigators were also requested to document the occurrence and intensity (severe or not) of dysphonia, dysphagia, neck muscle weakness and other.

Study size

The sample size was determined based on both the primary and exploratory objectives (prognostic factors for response). Considering an anticipated rate of responder of 50%, using an estimate for this proportion with a precision of 5%, the required sample size was determined to be 385 subjects (assuming a two-sided 95% confidence interval [CI]). When considering the objective related to the detection of prognostic factors (assuming Alpha=5%, Power=80%), in order to ensure the ability to detect odds ratio ≥2 and a probability to be exposed to any given level of a prognostic factor larger or equal to 1/3 (=imbalance), the required sample size is 366 subjects. Thus in order to ensure 385 evaluable subjects, 400 subjects were included in this study.

Statistical analyses

The safety population consisted of all subjects who received one BoNT-A injection, whereas the efficacy population comprised all subjects in the treated population for whom there were data for each of the four underlying variables for response. The responder analysis was

performed using the efficacy population and all secondary endpoints were assessed using the safety population.

The primary endpoint was summarised overall, and by each of the four criteria, as the percentage of responders as a point estimate and its associated 95% CI. Responder subgroup analyses were also performed to investigate response based on the following criteria: predominant component of head/neck rotation; BoNT-A preparations; duration of CD; previous BoNT-A use; dystonia localisation (head/neck, trunk, limbs); presence of tremor based on the TSUI scale; use of electromyography (EMG); and use of concomitant therapies at baseline.

As an exploratory analysis, a stepwise multivariate logistic regression analysis was performed on the efficacy population to assess prognostic factors for response using subgroup variables, as well as additional demographic and disease characteristics variables. Odds ratios (OR) with 95% CI estimated by the logistic model were calculated using the primary criteria; a lower 95% CI bound >1 indicated a significantly increased chance of being a responder.

No estimations were made for missing data and there was no controlling for confounding factors.

RESULTS

Subject population

Between 19 February 2009 and 12 February 2010, 404 subjects from 38 centres in 9 countries (Australia, Belgium, Czech Republic, France, Germany, The Netherlands, Portugal, Russia and the United Kingdom) were enrolled and followed in this study. A total of 379 subjects (93.8%) completed the study. The most common reason for not completing the study was loss to follow-up (3.2%; n=13); no subjects discontinued due to lack of efficacy.

The safety population included all subjects treated with BoNT-A (n=404), whereas the efficacy population included all subjects treated with BoNT-A for whom data were available for each of the four criteria for the primary endpoint (n=367).

Baseline demographic and disease characteristics are shown in Table 1. The majority of subjects were female (64.9%), aged 41–60 years (52.5%), and had suffered from CD for >1 year (90.9%). Nearly all of the subjects had sporadic CD (94.8%), and focaldystonia predominated (91.6%). In the few cases of segmental/multifocal dystonias, the upper limb was the most frequently impaired segment. The most common predominant component of CD was rotation (72.8%), followed by laterocollis (14.1%). The majority of subjects had secondary components (83.9%).

Table 1: Subject demographics and CD characteristics (safety population)

Demographic/characteristic		Total, n=404
Gender, n (%)	Male	142 (35.1)
	Female	262 (64.9)
Age (years), n (%)	18 to 30	18 (4.5)
	31 to 40	52 (12.9)
	41 to 50	105 (26.0)
	51 to 60	107 (26.5)
	61 to 70	81 (20.0)
	>70	41 (10.1)
Body weight (kg), mean (SD)		72.8 (14.9)
Duration of cervical dystonia, n (%)	<6 months	10 (2.5)
	6 months to <1 year	27 (6.7)
	1 to 5 years	140 (34.7)
	6 to 10 years	89 (22.0)
	11 to 20 years	84 (20.8)
	>20 years	54 (13.4)
Type of cervical dystonia, n (%)	Sporadic	383 (94.8)
	Familial	21 (5.2)
Location type, n (%)	Focal	370 (91.6)
	Segmental	20 (5.0)
	Multi-focal	9 (2.2)

	Generalised	5 (1.2)
Localisation, n (%)	Head/neck	404 (100.0)
	Trunk	13 (3.2)
	Upper limb	29 (7.2)
	Lower limb	6 (1.5)
Predominant component, n (%)	Rotation	294 (72.8)
	Laterocollis	57 (14.1)
	Tremor	20 (5.0)
	Retrocollis	12 (3.0)
	Shoulder elevation	8 (2.0)
	Anterocollis	4 (1.0)
	Jerk	4 (1.0)
	Lateral shift of column	3 (0.7)
	Sagittal shift of column	2 (0.5)
Secondary components present, n (%)	Yes	339 (83.9)
Most frequent combinations of predominant and secondary components, n (%)	Rotation and laterocollis	161 (39.9)
	Rotation and shoulder elevation	143 (35.4)
	Rotation and tremor	73 (18.1)
TWSTRS score at baseline, mean ± SD	Severity subscale Disability subscale Pain subscale Total score	19.5 ± 3.8 10.6 ± 5.9 6.6 ± 4.9 36.8 ± 10.7
Baseline tremor present	n(%)	191 (47.3)
CDIP-58 subscales scores[a], mean ± SD	Head and neck symptoms Pain and discomfort Upper limb activities Walking Sleep Annoyance Mood Psychosocial	50.6 ± 25.2 31.8 ± 27.8 26.1 ± 24.6 22.4 ± 26.7 23.0 ± 31.0 26.4 ± 27.7 21.6 ± 25.9 30.7 ± 28.2

[a]CDIP-58 n=99 (questionnaire in English, thus completed by English speaking patients only).

Treatment history

Most subjects had previously received a BoNT-A injection (84.9%).A minority of patients had prior history of treatment with BoNT-B (5.7%).Of the safety population, more than half of subjects (n=215; 53.2%) had previously received benzodiazepines for the treatment of CD and approximately one-third (29.7%) continued to receive these agents after BoNT-A treatment. Prior physical therapy was reported in 49.8% of subjects, but only 14.6% of subjects were receiving physical therapy at the inclusion visit. Analgesics had been previously taken by 40.8% of subjects, with 18.3% of subjects receiving analgesics at the inclusion visit.

Injection schemes

Physicians prescribed three BoNT-A preparations: Dysport (n=279, 69%), Botox (n=113, 28%) and Xeomin (n=12, 3%), independently from study enrolment, as per local clinical practice at the center. Subjects received Dysport and Botox at median doses of 500 and 160 units, respectively. Overall, 90% of patients received less than 1000 U of Dysport and 300 U of Botox. In total, the median number of injected muscles was four; of which, the most frequently injected muscles in both the Dysport and Botox groups were the splenius capitis, sternocleidomastoid and trapezius. For Xeomin the median dose was 200 units although small patient numbers make results difficult to interpret. Investigators used EMG during administration of at least one muscle in 185 subjects (46.0%).

Efficacy

Responder analysis

The percentage of subjects meeting the response criteria, as well as each of the individual response criteria, is shown in Figure 1. Three criteria out of four were achieved in the majority of patients, as shown by 97.5%, 73.6% and 69.8% of subjects achieving criterion of magnitude of effect, tolerance (absence of severe related AEs) and subject's CGI, respectively. A total of 49.3% of subjects achieved response based on the duration of effect criterion (≥12 weeks between inclusion and subject-rated waning of treatment effect). Overall, 28.6% (95% CI: 24.0% to 33.5%) of subjects were classified as responders to treatment.Evaluation of response by TWSTRS, tolerance and CGI improvement alone (i.e. exclusion of duration of effect) established 58.3% (95% CI: 53.1% to 63.4%) of subjects as responders.

Responder subgroup analysis

Analysis of the response criteria by subgroup is shown in Figure 2 and showed that there were variations in response, albeit these results were not statistically significant. Data

revealed that more subjects responded among subgroups presenting with laterocollis (41.7% versus 26.7% with rotation), without baseline tremor (33.2% versus 23.7% with tremor), and those not receiving concomitant medication at baseline (35.1% versus 22.8% receiving baseline concomitant medications).

Prognostic factors associated with response

The multivariate logistic regression showed that the most strongly associated factor to response wasage (<40 years; OR 3.9, p<0.05). Additional trends with a lower magnitude of association were observed (data not shown).

Secondary efficacy outcomes

Secondary efficacy outcomes are shown in Table 2. Subjects reported a notable improvement in TWSTRS total score and subscale scores over the course of treatment, as indicated by the percentage change in scores at each visit. Sixty-six of the 181 subjects (36.5%) with baseline tremor no longer presented with tremor at Visit 2. HRQoL improved following BoNT-A treatment, as demonstrated by decreases in all eight subscores of the CDIP-58 at Visit 2.

Table 2. Efficacy outcomes

	Visit 2	Visit 3
Percentage change in TWSTRS Score, mean ± SD	(n=374)	(n=380)
Severity subscore	–40.8 ± 25.1	–16.5 ± 22.3
Disability subscore	–36.3 ± 49.8	–6.6 ± 90.2
Pain subscore	–35.8 ± 49.9	–7.6 ± 72.6
Total score	–39.6 ± 26.6	–15.4 ± 27.0
Tremor	(n=375)	(n=380)
Subjects with improvement in tremor[a] with treatment, n (%)	66/181[b] (36.5)	41/178[a] (23.0)
CDIP-58 subscales scores, mean ± SD	(n=93[c])	–
Head and neck symptoms	26.1 ± 21.9	–
Pain and discomfort	20.5 ± 23.5	–
Upper limb activities	16.3 ± 19.9	–
Walking	15.3 ± 21.5	–
Sleep	12.3 ± 20.0	–
Annoyance	15.6 ± 23.9	–
Mood	18.9 ± 20.5	–

Psychosocial functioning	19.2 ± 23.6	–

[a]Improvement defined by presence of tremor at baseline and absence of tremor at subsequent visits.

[b]Subjects with data available at this timepoint and with tremor present at baseline.

[c]Questionnaire in English, thus completed by English speaking patients only.

Safety and tolerability

A total of 88 treatment-related AEs were reported during the study. Overall, 68 subjects (16.8%) experienced at least one treatment-related AE. Of the observed AEs, dysphagia was the most commonly reported (9.2%). Overall, ten treatment-related AEs were considered to be severe, with neck muscle weakness (n=4) being observed as the most common AE at this grade of severity. The incidence of AEs (severe and not severe) and dysphagia did not statistically differ between BoNT-A preparations (Figure 3).

DISCUSSION

In this non-interventional study of subjects with CD in routine practice, the majority of subjects were middle-aged women. These demographic data were in accordance with a typical population of subjects with CD.[15] TWSTRS and CDIP-58 scores at baseline reflected a population with moderate to severe CD severity.

Real-life data on response to BoNT-A in CD are relatively sparse,[16–18] and studies evaluating multidimensional definitions of response, in particular, are lacking. Therefore, the primary objective of this study was to estimate the rate of response following one BoNT-A injection cycle in real-life practice using a challenging multidimensional definition developed by an expert group of neurologists. To our knowledge, this is the first such non-interventional study to apply a consensus-based multimodal definition of response to a large real-world population of patients with CD treated with BoNT-A. In the interpretation of our findings, it should be borne in mind that clinical studies have commonly utilised a single or co-primary endpoint for example.[19,20] Thus, the requirement to achieve four primary endpoints within the multidimensional response definition proposed in this study represented a significant challenge. Notably, this ambitious definition for response was achieved by almost one-third (approximately 30%) of the 404 subjects who participated in this study. Although the magnitude of effect and subject satisfaction were both high and the number of treatment-related severe AEs was very low, the number of subjects with a duration of effect ≥12 weeks was relatively low. This is in contrast to published observations that suggest patients experience a duration of effect (mean or total) beyond 12 weeks, as shown in controlled trials of Dysport and Botox.[6,9] Considering three primary endpoints, that is with the exclusion of the duration of effect criterion, approximately 60% of patients achieved response. In the clinical experience of the expert group of neurologists, the level of response achieved with three or four co-primary endpoints is highly encouraging. Therefore, our novel findings indicate that measurements for the magnitude of effect, subject satisfaction and safety profile according to routine practice demonstrate good clinical response to BoNT-A in subjects suffering from CD. However, duration of effect such as defined in the study may require further confirmation due to its subjective nature. Waning of effect is a gradual process and therefore assessment for duration of effectbased on serial subject's CGI measurements (rather than depending on the patient reporting on waning of effect on a single specific date) may have been more appropriate. Regardless of these considerations, unrealistically high patient expectation and subjectivity may influence the perception of quick waning of effect. This highlights that, for some patients, this aspect is seen as a hurdle to response.

The subgroup analyses suggest that laterocollis as a predominant component, the absence of baseline tremor and absence of concomitant medication are factors that may be associated with higher response rates. Even if these data were not statistically significant,

they provide a good starting point for further evaluation. In particular, it would be interesting to establish whether the use of concomitant medication at baseline reflects a greater disease severity (as assessed with TWSTRS scores) or more co-morbidities associated with CD (e.g. anxiety, depression) that could interfere with the therapeutic effect of BoNT-A. With relevance to the former, data from this study suggest that the duration of CD (≤10 years versus >10 years) did not markedly influence the distribution of concomitant therapies (data not shown).

Efficacy findings confirm the value of BoNT-A as a treatment for CD symptoms. Notable improvements in mean TWSTRS scores were observed, as was improvement in tremor. It is recognised that HRQoL is compromised in CD, especially among women.[20] In this analysis of a largely female population, the decrease in subscores of the CDIP-58 (a more sensitive measure of clinical change than other frequently used HRQoL instruments[13] is consistent with previous reports in confirming the positive impact of BoNT-A on HRQoL when administered as a therapy for CD.[21,22]

BoNT-A was generally well tolerated in this study, with few reported severe AEs. In general, treatment-emergent side effects were consistent with the known safety profile of this treatment.[6] As observed in previous reports, the most common side effect of BoNT-A treatment was dysphagia.[6,20] Overall, this study highlights that no new safety concerns were raised with BoNT-A when used in routine clinical practice. For any given treatment, an acceptable level of tolerance is required to ensure continued treatment and subject compliance; hence the inclusion of tolerance as a response criterion. In total, 97.5% of subjects met the response criterion of no severe treatment-related AEs. It may be speculated that the presence of treatment-emergent side effects such as dysphagia could exert a negative impact on objective and subjective assessments of symptom improvement and ultimately response, but observed response rates of 73.6% (magnitude of effect) and 69.8% (subject's CGI) in this study would suggest otherwise.

Inherent to studies of this design (non-interventional), the lack of randomization, as well as the absence of a placebo-controlled group, means that confirmatory conclusions cannot be drawn. Moreover, the *a priori* defined duration of effect criteria was based on subject assessment of the waning of treatment effect. Thus, the subjective nature of this assessment has potential for bias resulting from patients' unrealistically high expectations from treatment; a hypothesis supported by the observation of maintained improvements in TWSTRS scores even at Visit 3.

CONCLUSIONS

This study reveals the CD subject demographics and BoNT-A response in a real-life clinical setting. Using a novel multimodal definition of response, this large-scale study showed that

the magnitude of effect, subject satisfaction and safety profile were well met and it was also felt that these were appropriate measures to assess BoNT-A response in CD subjects. This study also indicates possible predictive factors for BoNT-A in subjects with CD, but further research is required to confirm these in the prognosis of CD.

Acknowledgments: The authors would like to acknowledge the editorial assistance of Ogilvy Healthworld. Funding was provided by Ipsen.

The authors would also like to thank members of the INTEREST IN CD study group, who were:
Australia: Dr A Hughes, Dr K Kotschet, Dr D Williams, Dr V Fung; Belgium: Dr M van Zandijcke, Dr P Santens, Dr W van Landegem, Dr V Delvaux; Czech Rep: Dr E Ehler, Dr R Jech, Dr P Otruba, Dr M Bareš;France: Dr M Simonetta-Moreau, Dr S Soulayrol, Dr P M Burbaud, Dr A Kreisler, Dr C Vial, Dr M Borg, Dr S Sangla, Dr N Patte-Karsenti; Germany: Dr E Fleischer, Dr M Müngersdorf, Dr I Weimar, Dr R Pfister, Dr B Mohammadi, Dr I Nastos; Netherlands: Dr Laboyrie, Dr Douma;Portugal: Dr M J Rosas, Dr J Ferreira, Dr M Castelo Branco;Russia: Dr S Timerbaeva, Dr D Khasanova, Dr L Korenko, Dr G Belskaya;
UK: Dr P Moore, Dr M Kellet, Dr P Misra, Dr T Harrower.

Competing interests

Vijay P. Misra
Consultancies: *Ad hoc* consultant to Ipsen Pharma and Syntaxin Ltd..
Advisory Boards: Attended Ipsen Pharma Medical Advisory Boards.
Contracts: Contracts with Ipsen Pharma and Syntaxin Ltd. related to *ad hoc* Consultancies/Advisory boards.

Edvard Ehler
Grants: IGA Ministry of Health, Czech Republic.

Benjamin Zakine and Pascal Maisonobe
Employment: Ipsen.

Marion Simonetta-Moreau
Consultancies: Ipsen.
Employment: Hôpitaux de Toulouse and Paul Sabatier University.

Funding statement

This study was supported by Ipsen Pharma; employees (Benjamin Zakine and Pascal Maisonobe) of whom were involved in the design of the study and the subsequent preparation of this manuscript (writing and review).

Contributor statement

Vijay P. Misra was involved in the concept and design, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript review and critique, and final approval of manuscript.

Edvard Ehler was involved in the provision of study materials or patients, collection and assembly of data, manuscript review and critique, and final approval of manuscript.

Benjamin Zakine was involved in the concept and design, data analysis and interpretation, manuscript writing, manuscript review and critique, and final approval of manuscript.

Pascal Maisonobe was involved in the concept and design, data analysis and interpretation, manuscript writing, manuscript review and critique, and final approval of manuscript.

Marion Simonetta-Moreau was involved in the concept and design, provision of study materials or patients, manuscript review and critique, and final approval of manuscript.

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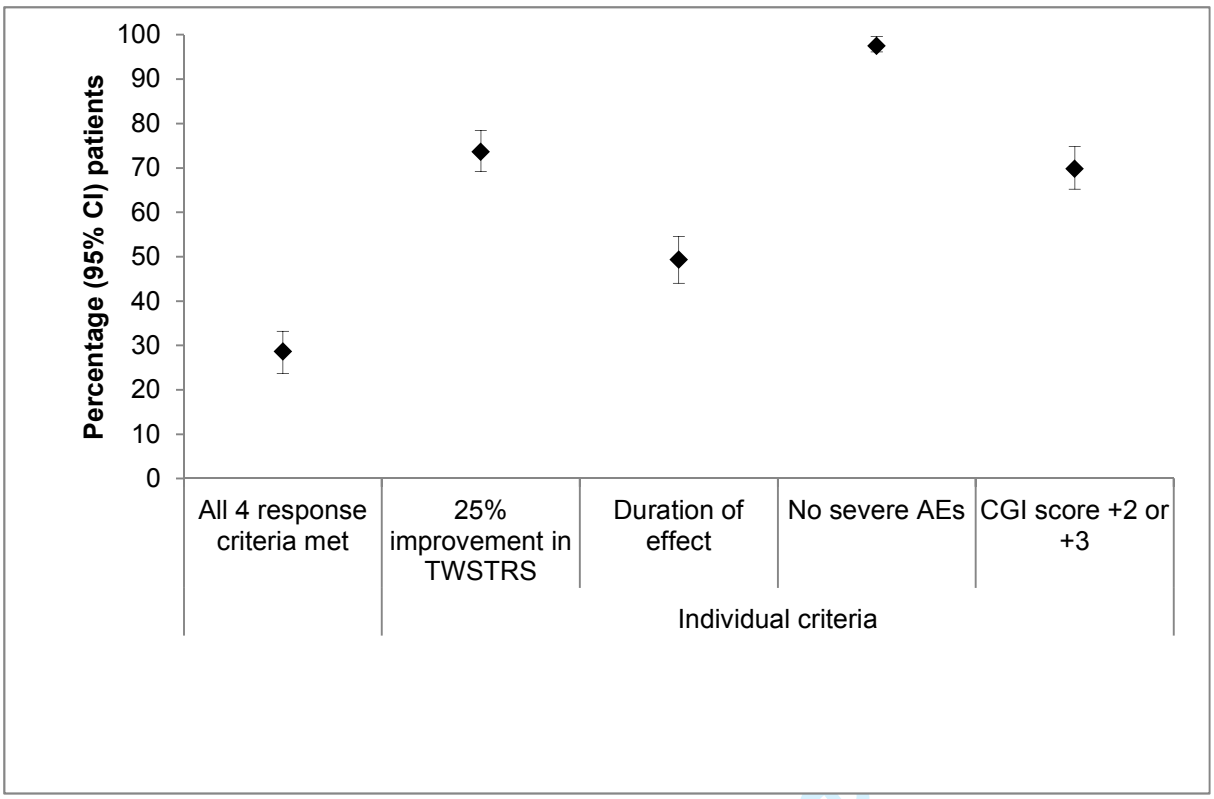
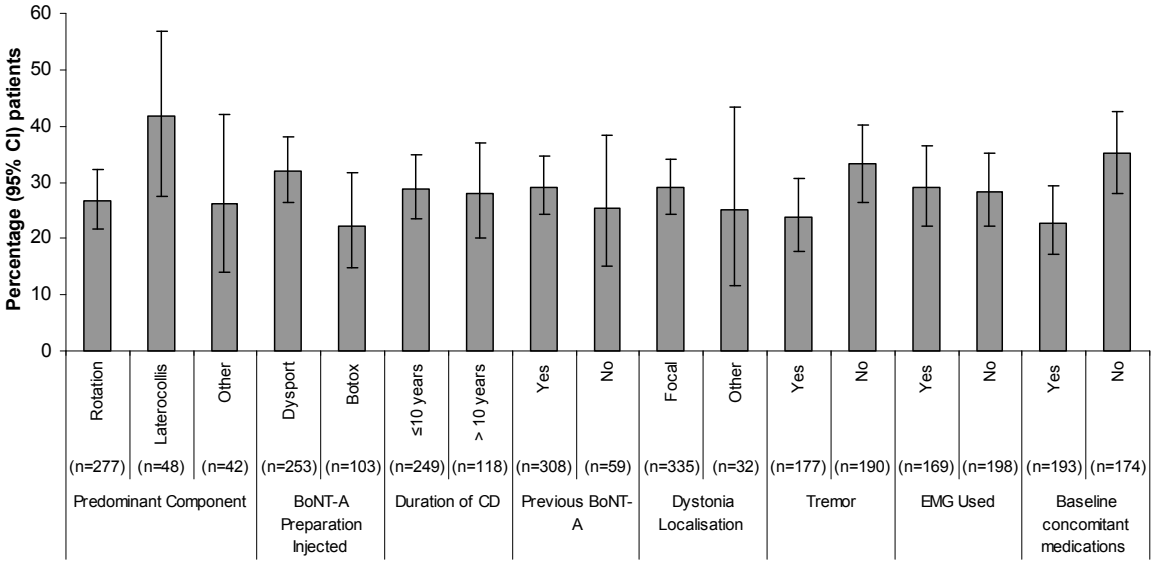
Figures

Figure 1: Responder analysis



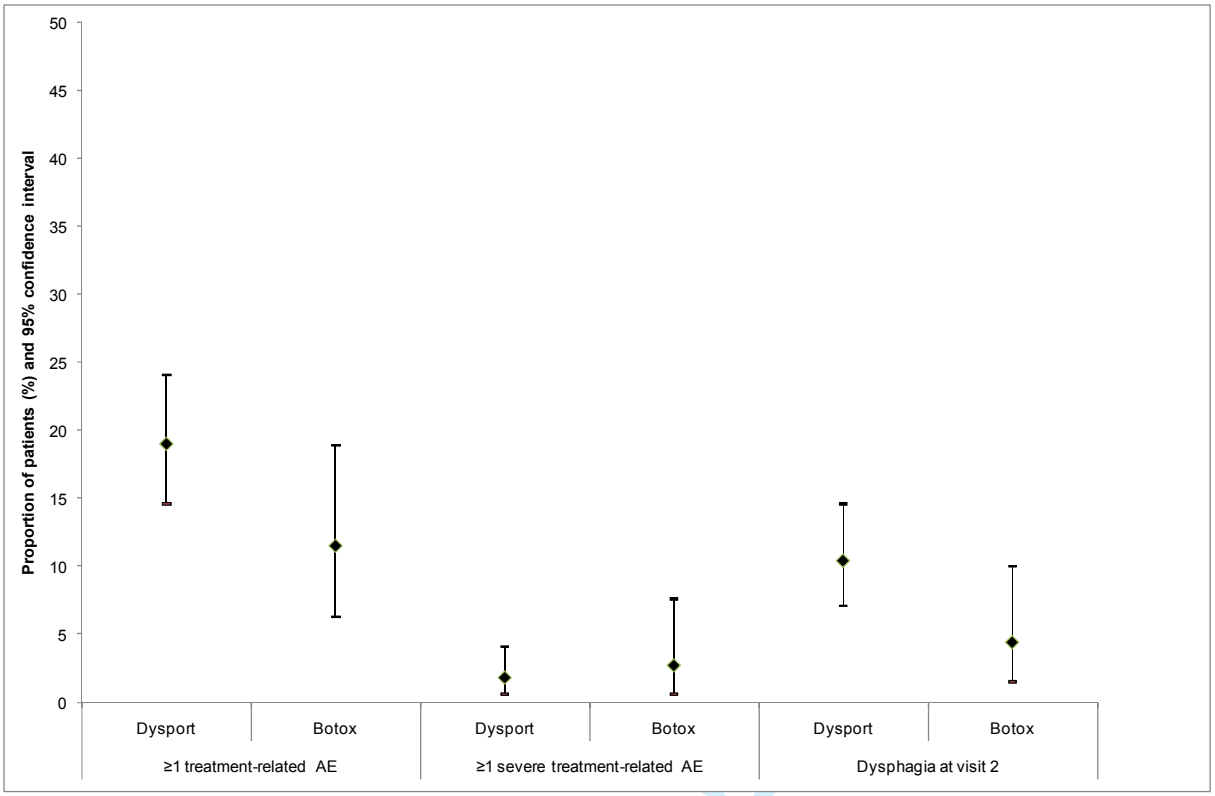
CI=confidence interval; TWSTRS=Toronto Western Spasmodic Torticollis Rating Scale; AEs=adverse events; CGI=clinical global improvement.

Figure 2: Subgroup analyses of responders (efficacy population)

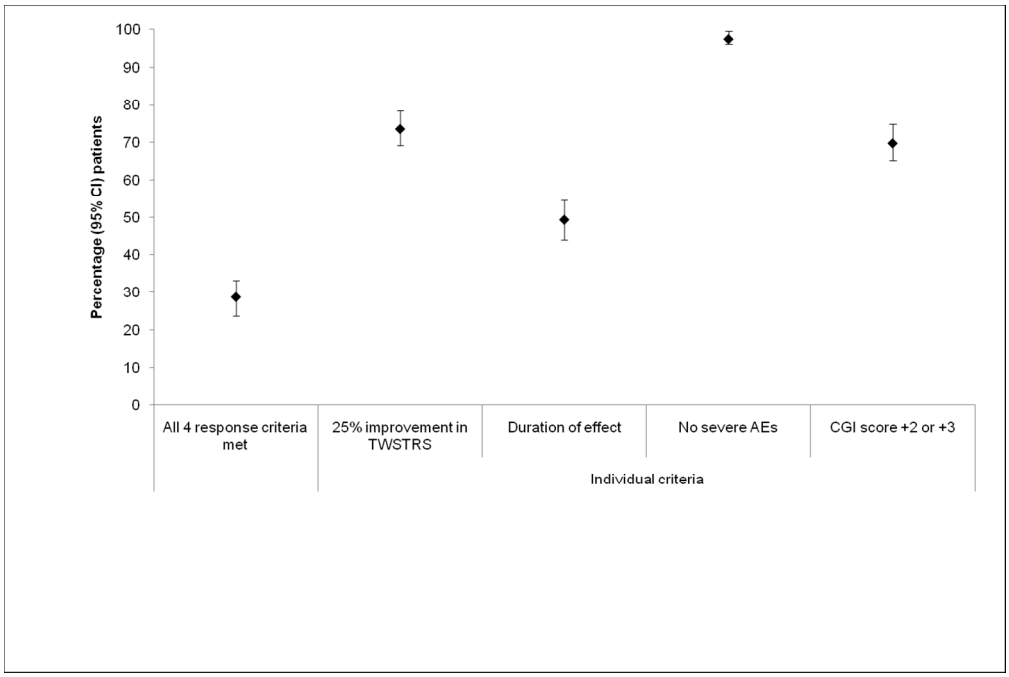


CI=confidence interval; CD=cervical dystonia; EMG = Electromyography; BoNT-A=Botulinum toxin A.

Figure 3: Occurrence of adverse events with frequently used BoNT-A preparation



BoNT-A=Botulinum toxin A; AE=adverse event.



Responder analysis
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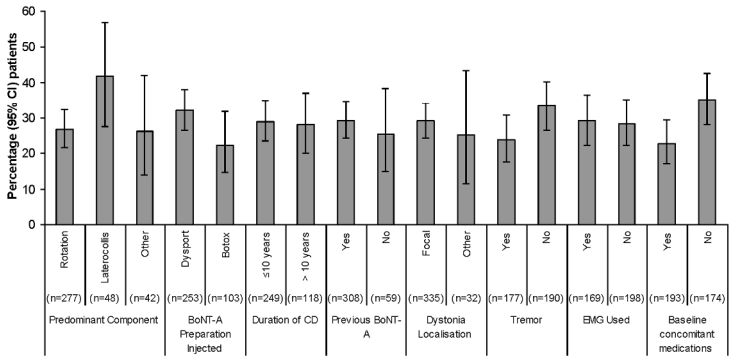

Subgroup analyses of responders (efficacy population)
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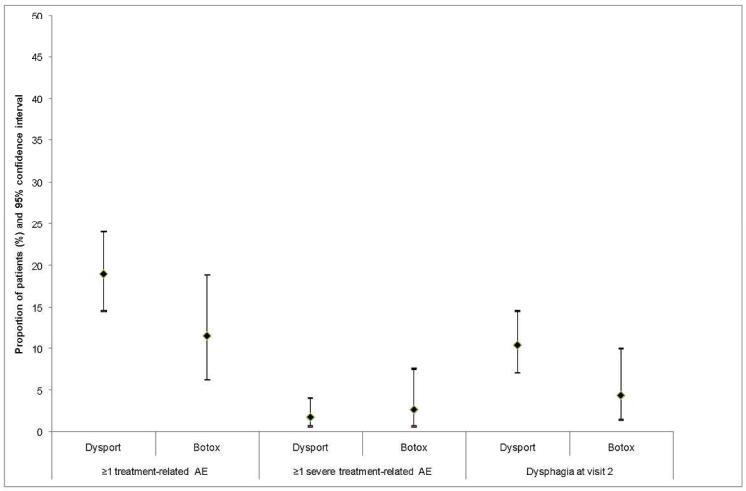

Occurrence of adverse events with frequently used BoNT-A preparation
297x210mm (200 x 200 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract - yes
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found- yes
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported- yes
Objectives	3	State specific objectives, including any prespecified hypotheses - yes
Methods		
Study design	4	Present key elements of study design early in the paper- yes
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection- yes
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up- yes
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable –these data are not relevant
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group - NA
Bias	9	Describe any efforts to address potential sources of bias - yes
Study size	10	Explain how the study size was arrived at – was there a sample size calculation? Yes
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding? No control for confounding factors
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed Missing data handling was addressed in the SAP (no estimation was made)
		(*d*) If applicable, explain how loss to follow-up was addressed - NA
		(*e*) Describe any sensitivity analyses - NA
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed -yes
		(b) Give reasons for non-participation at each stage - NA
		(c) Consider use of a flow diagram - NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders - yes
		(b) Indicate number of participants with missing data for each variable of interest - yes
		(c) Summarise follow-up time (eg, average and total amount) -NA
Outcome data	15*	Report numbers of outcome events or summary measures over time - YES

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included - Not relevant
		(*b*) Report category boundaries when continuous variables were categorized- Not relevant
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period- Not relevant
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses- Not relevant
Discussion		
Key results	18	Summarise key results with reference to study objectives - yes
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias - yes
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence - yes
Generalisability	21	Discuss the generalisability (external validity) of the study results -yes
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - yes

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.