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Factors influencing secondary non-response to botulinum toxin type A injections in cervical dystonia

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ABSTRACT

Background: The development of secondary non-response (SNR) to botulinum neurotoxin type-A (BoNT-A) is considered a key issue in the management of cervical dystonia (CD). This case-controlled study was performed to systematically identify factors influencing SNR during BoNT-A therapy.
Methods: This was a retrospective, international, non-interventional study of CD patients. Patients with SNR were matched with up to three responder patients (control) on the basis of duration of therapy and number of injection cycles. Factors influencing the development of SNR were screened using a univariate logistic regression model and confirmed using a multivariate conditional logistic regression model.
Results: 216 patients were enrolled, and 201 (SNR = 52; responder = 149) were matched and subdivided into blocks (doublets, triplets or quadruplets). At baseline, a significantly higher proportion of SNR patients had received previous or concomitant therapies ($p = 0.038$) and surgery for CD ($p = 0.007$) compared with controls. Although disease severity at onset was similar between groups, a significantly higher proportion of SNR patients experienced severe CD at the time of SNR compared with controls at the last documented visit. Multivariate analyses identified five factors that were significantly associated in predicting SNR (odds ratio [OR] > 1 indicated higher chances for being SNR): previous surgical procedure for CD (OR 9.8, $p = 0.013$), previous BoNT-A related severe adverse event (AE) (OR 5.6 $p = 0.027$), physical therapy (OR 4.6, $p = 0.028$), neuroleptic use (OR 3.3, $p = 0.019$) and average BoNT-A dose (OR 2.7, $p = 0.010$).
Conclusions: These findings suggest that SNR may not reflect true pharmacological resistance to BoNT-A therapy, but may be related to underlying disease severity.

1. Introduction

For the majority of patients, cervical dystonia (CD) is a chronic illness that lasts for the rest of the patient's life, and therefore requires an effective long-term management strategy [1]. Muscle chemodenervation with targeted injections of botulinum neurotoxin type A (BoNT-A) is the recommended first-line symptomatic treatment for CD [2,3]. The efficacy and safety of three of the commercially available BoNT-A preparations (abobotulinumtoxinA, Ipsen Biopharm Ltd., Wrexham, UK; incobotulinumtoxinA Merz Pharmaceuticals, Frankfurt am Main, Germany and onabotulinumtoxinA Allergan, Inc., Irvine, CA, USA) have each been well established with Level A recommendations for use in CD [4]. Recent systematic reviews of long-term studies have also concluded that treatment effectiveness is usually sustained and that BoNT-A preparations not only provide symptomatic relief but may also modify the natural history of CD, for example by reducing the risk of contractures [5,6].

The development of secondary non-response (SNR), or loss of a previously good clinical response, to BoNT-A treatment is

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considered a key clinical issue and is cited as the key reason for switching patients to a botulinum neurotoxin type B preparation [2]. Once considered a result of neutralizing antibody (NAb) formation against the neurotoxin, it is now understood that this does not fully account for the development of a SNR and that development of NAbs does not necessarily mean that the patients will develop SNR [7,8]. However, there has been little systematic work done to understand the predictors for developing SNR and, depending on the differing definitions of SNR, the incidence in long-term trials has ranged from 3% to 7.5% [9–11]. We have previously reported a survey of neurologist clinical practice that was performed to find a clinically-driven definition of SNR. On the basis of the results, SNR was defined as *"insufficiently improved posture after three or more unsuccessful injection cycles in CD patients previously achieving satisfactory results"* [12]. Using this clinical definition, the objective of the present study was to identify in a large cohort of CD patients, factors influencing SNR during BoNT-A therapy.

2. Methods

2.1. Study design

This was a post-marketing, retrospective, case-controlled, international, multicentre, non-interventional study. The study was approved by the Independent Ethics Committee/Institutional Review Board as applicable in each of the seven participating countries and was conducted in compliance with guidelines for Good Pharmacoepidemiology Practices [13].

Each investigator was asked to select one SNR patient (defined as patients with insufficiently improved posture after three or more unsuccessful injection cycles) and three corresponding responder (control) patients (maintaining sufficiently improved posture) using medical files only, in accordance with a randomized alphabetical selection method. Non-responders were matched to responders on the basis of overall duration of therapy and overall number of injection cycles. Data for SNR patients was taken from the time when SNR was reported and for responders from the time of last documented visit (LDV). The time interval between SNR or LDV and data collection was originally not permitted to exceed two years, but this was extended to five years in order to aid recruitment of SNR patients. In line with routine practice, all assessments were made at the time of injection.

Adult patients with idiopathic CD without any secondary structural deformities were eligible for the study. All patients had to have had treatment with BoNT-A for at least one year, with no less than four BoNT-A injection cycles and had to have demonstrated a positive response to BoNT-A (defined as sufficiently improved CD outcome, irrespective of the clinical tool or scale used by the physician). SNR case patients also had to have had an insufficiently improved posture after three consecutive injection cycles. Incomplete data was considered a valid reason for the exclusion of any patient. All eligible patients provided informed consent for this retrospective study; no other inclusion/exclusion criteria were specified.

2.2. Statistical analyses

To determine the minimum sample size, a binary outcome variable and a two-tailed test with significance level of 0.05 and a power of 80% was used. Assuming 10% of patients with incomplete data, it was determined that a total of 224 patients, split as 168 controls and 56 SNR, would allow for the detection of associated factors with an odds ratio (OR) $\geq$3 (when the proportion of controls expected to be exposed varied from 0.2 to 0.6).

The primary analysis was performed on the enrolled matched population, referring to patients analyzed as a quadruplet (one SNR patient matched to three controls), a triplet (one SNR patient matched to two controls) or as a twin (one SNR patient matched to one control).

2.2.1. Logistic regression analysis to identify factors associated with SNR

A conditional logistic regression model was used as the primary statistical analysis to identify the associated factors for SNR. The outcome of the model was whether the patient was a case (SNR) or control (responder). A two-step procedure was applied: where step 1 was a univariate conditional logistic regression analysis of 27 potential factors identified *a priori*, with duration of BoNT-A treatment and number of injection cycles included as strata. All variables with a *p*-value of rejecting the null hypothesis of $\leq$10% in the univariate analysis were to be included in step 2. In order not to introduce in the final model variables strongly correlated with each other, the relationship between the pre-selected variables were tested (via either Spearman correlation or Chi^2 test or ANOVA depending on the nature of the concerned variables). In case of strongly correlated variables (rho $\geq$0.60) or *p* value <0.05, only the variable that brings most information to the model in the univariate analysis (i.e. with the smallest value of the "-2 LOGL" criterion) was included in the multivariate model. In addition, the decision to select one variable rather than another was based on the amount of missing data and the clinical relevance of the studied variable. This step defined the set of selected variables used to construct the multivariate model. The eight covariates identified by the step 1 univariate analysis are listed in detail in Supplementary Table S1 and included CD presentation at time of SNR, previous BoNT-A therapy and history of BoNT-A injection cycles. Accordingly, the multivariate logistic model included all retained variables from the univariate analysis for which no strong association was evidenced. The amount of missing data and the clinical relevance of the variables were also considered in the selection of variables to be kept among correlated variables. The final model was obtained by using a stepwise selection (entry/stay levels = 5%). Estimated OR and their 95% confidence intervals (CI) were determined for each variable that was kept in the final model.

Sensitivity analyses were also conducted with the *per protocol* population (all patients with a history of CD longer than one year and with an interval of time between data collection and LVD of less than five years). To further assess the robustness of the results the analyses were replicated using the more conservative quadruplet population (quadruplet enrolled matched population and quadruplet *per protocol* matched population).

2.2.2. Safety analysis

No collection of the nature of adverse events (AEs) was planned in this study. Only the presence of previous occurrence of any serious AEs related to BoNT-A therapy was recorded without further details.

3. Results

3.1. Patient disposition and baseline characteristics

Patient enrollment took place in seven countries (Italy, Poland, Portugal, Romania, Russia, Spain and Thailand) between September 2010 and July 2012.

A total of 216 patients from 28 sites were enrolled and stratified by country; no country effect was evidenced. The majority (SNR = 52; responder = 149; total = 201) were matched and subdivided into blocks (2 twin, 3 triplet and 47 quadruplet sets) to form the enrolled matched population. The remaining 15 patients were unmatched (Fig. 1). A total of 209 patients met criteria for the per protocol population.

Patient demographics and clinical characteristics for the enrolled matched population are summarized in Table 1. The mean age of the enrolled matched SNR group and enrolled matched control group was 52.3 and 53.4 years, respectively and the mean duration of CD was 10.2 years for SNR patients and 9.5 years for controls. Most patients presented with rotation or laterocollis. Associated symptoms included sensory tricks (SNR 48%, control 53%), tremor (42% in both groups) and jerk (SNR 17.3%, control 19%).

A significantly higher proportion of SNR patients had received previous or concomitant therapies (90% vs. 78%; $p = 0.038$) and surgery for CD (12% vs. 1%; $p = 0.007$) compared with the control group. The higher use of previous or concomitant therapies appeared to be driven by increased use of neuroleptics or physical therapy in SNR patients. Although severity of the disease as judged by the investigator was similar for both groups at disease onset, a significantly higher proportion of SNR patients were reported to have severe or very severe CD at the time of SNR compared with controls at LDV.

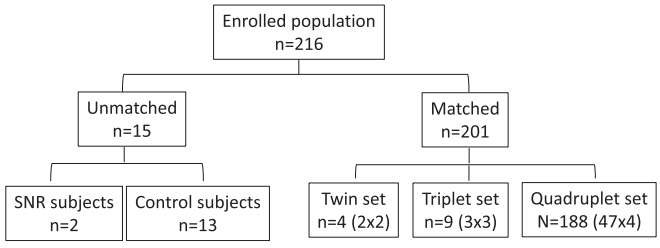

Fig. 1. Patient flow of SNR and control patients in the enrolled population.