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Cost minimization analysis of BoNT-As in the treatment of upper limb spasticity and cervical dystonia

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ABSTRACT

Objective: Botulinum toxin type A (BoNT-A) injections are recommended for the management of upper limb spasticity (ULS) and cervical dystonia (CD). The main aim of this cost minimization analysis (CMA) was to compare the annual cost per patient for three BoNT-As (Botox®, Dysport® and Xeomin®) in the treatment of ULS or CD in Italy. A budget impact analysis (BIA) was also conducted.

Methods: The CMA was conducted from the perspective of the Italian National Health Service. Only direct medical costs (BoNT-A and standard therapy) were considered. By using a Delphi panel of twelve Italian Experts in the treatment of ULS and CD, data was collected about BoNT-As (dose, number of administrations and acquisition price) and standard therapy (concomitant medications, visits, Day-Hospital, hospitalizations, etc.). Costs were assessed in Euros 2014. The BIA was conducted to evaluate the pharmaceutical expenditure for the three BoNT-As on a five-year time horizon. A sensitivity analysis was conducted.

Results: The mean annual cost per patient with ULS was €1,840.20 with Dysport®, €2,067.12 with Botox® and €2,171.05 with Xeomin®. The mean annual cost per patient with CD was €1,353.79 with Dysport®, €1,433.12 with Botox® and €1,503.60 with Xeomin®. In the time horizon considered, the substitution process of Botox® and Xeomin® by Dysport® would result in a total saving of €620,000 when treating ULS and a total saving of €481,000 in the case of CD. Sensitivity and probabilistic analyses showed the robustness of results.

Conclusions: From the Italian National Health Service's perspective, Dysport® appears to be the cost-saving therapeutic option compared with Botox® and Xeomin® in the treatment of ULS or CD.

Keywords: BoNT-A, Cervical dystonia, Cost-minimization analysis, Upper limb spasticity

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Introduction

Botulinum toxin type A (BoNT-A) is recommended as pharmacological treatment, along with physical therapy and postural control management, in the treatment of upper limb spasticity (ULS) and cervical dystonia (CD) (1-4).

When injected in the muscle, botulinum toxin acts pre-synaptically blocking the release of acetylcholine

neurotransmitter in the neuromuscular junction, causing a reduction of the contraction force (5). This action allows the muscles to relax, restoring normal posture. The use of BoNT-As is frequently associated with a significant improvement in patients' health conditions (pain intensity, muscle tone, lessened disability) and quality of life (4, 6-12).

The main formulations of BoNT-A currently available in Italy are Botox® (Allergan SpA), Dysport® (Ipsen SpA) and Xeomin® (Merz Pharma Italia srl). The respective authorizations for use in the treatment of ULS and CD have been obtained by submitting to the competent Agency three different registration *dossiers*, each drawn up in the form of a Full Application, i.e. presenting the results of pharmaceutical studies, preclinical studies and clinical trials. As a result of these three different registration *dossiers* Botox®, Dysport® and Xeomin® constitute three distinct originator drugs (13).

Apart from the regulatory aspects, the three BoNT-As are also characterized by significant differences in terms of manufacturing process, efficacy, distribution (persistence in the application site) and dose-response curve, as well as in structure, molecular weight, excipients, purification processes and storage methods (14-16). Because of these differences, the units of each BoNT-A are not interchangeable and the number of units recommended for each indication is specific for each preparation (17). Thus, the clinician's choice in determining which BoNT-A to administer is often complex.

As efficacy and tolerability seem to be strictly dose-dependent (8-11, 18-21), in a perspective of containment of pharmaceutical expenditure, the simultaneous presence of three different pharmacological alternatives for the treatment of ULS or CD determines the need to provide, in support of clinicians' decision-making process, at least an estimate of their economic impact on the Italian National Health Service (INHS). Pursuing this objective, this economic assessment was conducted to evaluate which BoNT-A (Botox®, Dysport® or Xeomin®) determines the most efficient allocation of the economic resources available to the INHS in the treatment of ULS and CD. Additionally, for the purpose of estimating the impact of these choices on pharmaceutical expenditure, a Budget Impact Analysis (BIA) was conducted (22).

Methods

Analysis technique

Since it seems to be more appropriate to speak of differences in dosages rather than in efficacy and tolerability (8-11, 17-20), we chose to conduct this comparison in the form of a Cost Minimization Analysis (CMA) and to focus solely on the costs of treatment associated with the use (dosage) of the three botulinum toxins type A.

Study design

Cost minimization analysis

The comparison between the botulinum toxins – expressed in terms of average annual cost per treated patient – was made possible through the development of an Excel® model. The CMA was conducted from the INHS's perspective, considering solely the direct medical costs such as botulinum therapy and standard therapy. The latter consists of concomitant drugs (anticholinergics, anticonvulsants, analgesics, etc.), interventions by specialists (neurologist, physical therapist, physiatrist, etc.), rehabilitation therapies (electromiography, electrostimulation, ultrasound, etc.) and other healthcare services (Day-Hospital, hospitalizations, CT scans, etc.). The cost estimate refers to 2014, while the analysis time horizon is 12 months, commensurate to the objective of estimating an average annual cost per patient.

Budget impact analysis

The budget impact analysis has been conducted with the objective of building a scenario representing the five-year evolutionary trend of pharmaceutical expenditure for the three botulinum toxins. This was done using:

- cost data associated to pharmacological treatment with BoNT-A only,
- available epidemiological data to estimate the size of the cohorts of patients with ULS or CD eligible for treatment with BoNT-A, and
- the market shares of the three BoNT-As (estimated on the basis of the number of vials purchased in the last six months by healthcare facilities).

The estimate of the number of patients with ULS or CD eligible for treatment with BoNT-A in the five-year period was carried out according to a rather complex process. The starting point was the determination of the general population in the first year of analysis, corresponding to the resident Italian population on 1 January 2013 (ISTAT data). The evolution of the size of the general population over the next four years was determined by applying a constant average annual growth rate of 0.49%; this rate was calculated as a ratio of the resident Italian population on 1 January 2012 to the resident population on 1 January 2013.

The cohort of patients with CD eligible for treatment with BoNT-A was determined by applying to the general population, for each of the five years, a constant prevalence rate of cervical dystonia of 0.01375% (23); it was then assumed that only 84% of these patients could be treated with one of the three BoNT-As (24).

The second cohort of patients eligible for treatment with BoNT-A was estimated considering stroke as the only cause of ULS. First, a prevalence rate (1.47%) was applied to the general population to estimate the number of subjects with stroke (24). Subsequently, the number of subjects with stroke who could develop ULS was estimated (17% of the population with stroke). Lastly, it was assumed that 2.45% of these could be treated with a BoNT-A (24).

The two cohorts of patients estimated as described above were then subdivided according to their respective market shares: the number of patients receiving treatment with Botox®, Dysport® and Xeomin® year by year was thus determined. The market shares for the two investigated indications were estimated by a group of experts (see section "Healthcare resources and unit costs"). In the base scenario (Scenario A) market shares remained constant for all five

years. However, because the objective of the BIA was to determine the economic impact resulting from a greater use of botulinum toxin with the lowest average annual cost per patient, a new scenario was created (Scenario B), different from the base case, in which the market share of Dysport® increased compared to those of the other two BoNT-As, which instead decreased proportionally. In building Scenario B, the annual substitution effect of Dysport® was assumed to be 6 percentage points, balanced by an equal reduction of 3 percentage points for each of the other two toxins.

Healthcare resources and unit costs

To determine the healthcare resources used by patients with ULS and CD, and the respective unit costs, a group of experts were administered two questionnaires, one for upper limb spasticity and the other for cervical dystonia, specifically prepared by a board consisting of two leading experts. These data were collected using the Delphi technique, based on a structured interaction between experts and researchers (25, 26). First, a series of experts was identified on the basis of the following criteria: i) representative of the national territory, and ii) long-standing experience in the treatment of ULS and/or CD. These experts were then contacted via e-mail to explain the purposes and methodology of the data collection process, and to inquire about their willingness to participate. All the twelve experts who were contacted accepted to participate in the data collection project.

Each of the experts who confirmed their participation was sent two electronic questionnaires (ULS and CD) structured for data collection. The questionnaires were subdivided into three sections: the first and second sections were aimed at collecting data to determine the average annual cost per patient, while the third section was designed to estimate the market shares of the three BoNT-As (Budget Impact Analysis). In the first section, the experts were asked to indicate for each of the three BoNT-As – based on their experience with the patients treated in their centres – the average dose per treatment (expressed in units, U), the average number of weeks to the next treatment, and the cost incurred by the hospital pharmacy (ex-factory price net of mandatory discounts and any additional discounts granted by the marketing authorization [MA] holder to the healthcare facilities) to purchase one 500 U vial of Dysport®, one 100 U vial of Botox®, and one 100 U vial of Xeomin®. The selected dose units are those most commonly used in clinical practice. A scenario without drug wastage (full utilization of vial contents) has been considered to evaluate the cost of treatment of the three BoNT-As. In the second section, aimed at collecting data on healthcare resources used by standard treatment, to be added to the costs of botulinum toxin, the experts were asked to indicate:

- for the concomitant pharmacological therapy (anticonvulsants/analgesics, myorelaxants and other drugs)
  - the average percentage of use per patient,
  - the average dose per day of treatment, and
  - the average number of days per month of treatment;
- for specialist interventions (physiatrist, physical therapist, neurologist, etc.)
  - the average percentage of use per patient,
  - the average number of healthcare services provided during the year, and
  - the unit cost;
- for rehabilitation therapies (electromyography, electrostimulation, etc.) and other healthcare services (hospitalizations, Day-Hospital, etc.)
  - the average percentage of use per patient,
  - the average number of healthcare services provided during the year, and
  - the unit cost.

Consumptions related to concomitant pharmacological treatments were calculated on the basis of the respective purchase prices paid by the INHS, while all the other consumption items considered in the questionnaires were determined as average costs calculated on the basis of the unit costs (regional tariffs) indicated by the experts. In the second section of the questionnaire, the data collection was structured so as to exclude the possibility of differentiating standard treatment consumptions according to the administered botulinum toxin, and therefore assuming equal costs for Botox®, Dysport® and Xeomin®.

Lastly, in the third section of the case report form (CRF), in order to determine market shares necessary to conduct the BIA, the experts were asked to indicate (on the basis of the vials purchased by the hospital pharmacy in the last six months) the average consumption percentage for Dysport®, Botox® and Xeomin® in their respective centres.

In accordance with the Delphi methodology, the completed questionnaires were processed and prepared in the form of a first summary of results (first round), and submitted to a subsequent evaluation by the experts. Specifically, in this second round, the experts were asked to confirm or correct the data entered in their questionnaire, comparing them against those presented in the summary document. The values indicated by the experts on the first summary document (second round) were then set out as final data collection document. The average time provided for completion of the questionnaires and subsequent re-analysis was one month for each of the two rounds.

Sensitivity analysis

A series of univariate one-way analyses were conducted in order to evaluate the validity of the results of the Cost Minimization Analysis and Budget Impact Analysis base case in response to changes in the values of the parameters used. Specifically, in the univariate analysis the average base case values were changed one at a time with the respective median values for the dose per treatment, the time to next treatment and the cost per vial. As the vials price was also determined on the basis of information provided by the experts, it was deemed appropriate to repeat the CMA and the BIA replacing the base-case average price per vial with the ex-factory price net of the discounts required by law (Botox®: €129.05 for a 100 U vial; Dysport®: €175.32 for a 500 U vial; Xeomin®: €129.05 for a 100 U vial). Lastly, with reference to the BIA only, two additional scenarios were presented in which the effect of the substitution by Dysport® was increased to 8 and 12 percentage points per year.

Results

The distribution by geographic area (North, Centre, South and Islands) of the experts participating in the data collection reflects that of the Italian population, with minimal deviations (Tab. I). All twelve experts who were consulted completed the respective questionnaires concerning upper limb spasticity, while the percentage of completion of the cervical dystonia questionnaires was 83% (10 out of 12) because two experts included did not treat patients for this indication.

CMA results

Tables II and III present the detailed results of the comparison between the three botulinum toxins type A (Dysport®, Botox® and Xeomin®) expressed in terms of average annual cost per treated patient. For both the indications considered, upper limb spasticity and cervical dystonia, Dysport® was associated with the lowest annual average cost per treated patient. The difference compared to Botox® and Xeomin® is more significant in the management of ULS (ULS: -€226.88 compared to Botox® and -€330.81 compared to Xeomin®; CD: -€79.34 compared to Botox® and -€149.82 compared to Xeomin®). As the standard therapy was assumed to be the same for all three BoNT-As, the differences in average treatment costs are attributable solely to the administered botulinum therapy.

TABLE I - Geographic distribution of experts participating in data collection

Geographic areas	Experts		Italian population (× 1,000)*	
	no.	%	no.	%
North	6	50%	27,383	46%
Centre	2	17%	11,681	20%
South and Islands	4	33%	20,621	34%
Total	**12**	**100%**	**59,685**	**100%**

*Resident population at January 1, 2013.

TABLE II - Average annual cost per treated patient: ULS

Upper limb spasticity			
Cost drivers	**Dysport®**	**Botox®**	**Xeomin®**
Botulinum toxin	€700.63	€927.51	€1,031.44
Standard treatment	€1,139.61	€1,139.61	€1,139.61
- concomitant drugs	*€168.27*	*€168.27*	*€168.27*
- specialists	*€565.11*	*€565.11*	*€565.11*
- rehabilitation therapies	*€281.20*	*€281.20*	*€281.20*
- other healthcare services	*€125.03*	*€125.03*	*€125.03*
Total	**€1,840.24**	**€2,067.12**	**€2,171.05**
Difference vs Dysport®		**+€226.88**	**+€330.81**

TABLE III - Average annual cost per treated patient: CD

Cervical dystonia			
Cost drivers	**Dysport®**	**Botox®**	**Xeomin®**
Botulinum toxin	€668.87	€748.20	€818.68
Standard treatment	€684.92	€684.92	€684.92
- concomitant drugs	*€136.07*	*€136.07*	*€136.07*
- specialists	*€135.44*	*€135.44*	*€135.44*
- rehabilitation therapies	*€374.72*	*€374.72*	*€374.72*
- other healthcare services	*€38.68*	*€38.68*	*€38.68*
Total	**€1,353.79**	**€1,433.12**	**€1,503.60**
Difference vs Dysport®		**+€79.34**	**+€149.82**

TABLE IV - Average dose, average time to next treatment and average cost per vial: ULS

Upper limb spasticity			
Botulinum therapy	**Dysport®**	**Botox®**	**Xeomin®**
Average dose per session (U)	**661**	**218**	**263**
- median	*580*	*227*	*264*
- std. dev.	*290*	*73*	*76*
- min	*348*	*100*	*120*
- max	*1350*	*360*	*350*
Time to next treatment (no. of weeks)	**15.3**	**14.7**	**14.6**
- median	*16.0*	*15.4*	*14.9*
- std. dev.	*2.5*	*2.8*	*2.9*
- min	*10.0*	*10.0*	*11.0*
- max	*18.2*	*18.4*	*18.3*
Average cost per vial (€)	**€155.54**	**€120.14**	**€110.17**
- median	*€147.68*	*€117.54*	*€113.85*
- std. dev.	*€16.13*	*€4.99*	*€10.97*
- min	*€140.00*	*€116.14*	*€95.45*
- max	*€175.33*	*€129.05*	*€122.80*
Average cost per session (€)	**€205.62**	**€261.91**	**€289.75**

U = Unit.

Tables IV and V provide details, for ULS and CD respectively, of the average dose administered per treatment, the average number of weeks between treatments, the average cost per vial and the average cost per session (dose administered per treatment) of Dysport®, Botox® and Xeomin®.

With reference to the average cost of standard therapy in the treatment of ULS, specialist interventions account for the greatest portion (49.6%), followed by rehabilitation therapies (24.7%), concomitant drugs (14.8%) and other healthcare services (11.0%) (Fig. 1). Over 90% of the cost of specialist interventions is taken up by physical therapy sessions. Botulinum toxin injections cover approximately 60% of the total cost of rehabilitation therapies, while among

TABLE V - Average dose, average time to next treatment and average cost per vial: CD

Cervical dystonia			
Botulinum therapy	**Dysport®**	**Botox®**	**Xeomin®**
Average dose per session (U)	**538**	**148**	**178**
- median	*562*	*142*	*180*
- std. dev.	*145*	*48*	*50*
- min	*326*	*80*	*90*
- max	*750*	*245*	*245*
Time to next treatment (no. of weeks)	**12.7**	**12.4**	**12.2**
- median	*12.3*	*12.2*	*12.0*
- std. dev.	*1.5*	*1.6*	*1.5*
- min	*10.0*	*10.0*	*10.0*
- max	*15.0*	*15.0*	*15.0*
Average cost per vial (€)	**€151.58**	**€120.20**	**€107.90**
- median	*€145.23*	*€117.54*	*€104.50*
- std. dev.	*€14.62*	*€5.23*	*€10.59*
- min	*€140.00*	*€116.14*	*€95.45*
- max	*€175.33*	*€129.05*	*€121.08*
Average cost per session (€)	**€163.10**	**€177.90**	**€192.06**

U = Unit.

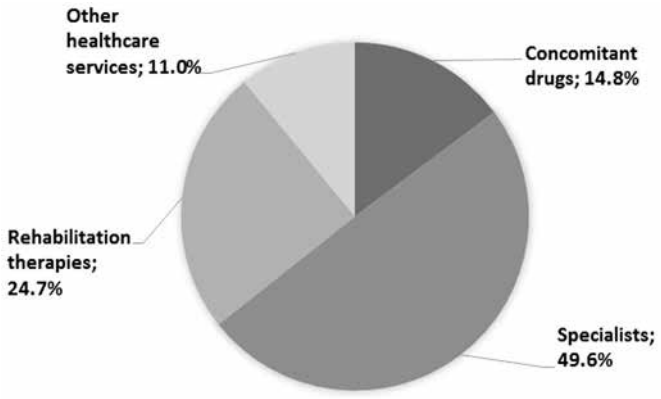

Fig. 1 - Standard upper limb spasticity (ULS) treatment: incidence of cost drivers.

concomitant drugs myorelaxants account for 90% of the expenditure.

In cervical dystonia, the main cost related to standard treatment is represented by rehabilitation therapies (54.7%), followed by concomitant drugs (19.9%), specialist interventions (19.8%), and other healthcare services (5.6%) (Fig. 2). Here again, the highest percentage (approximately 80%) of the costs related to rehabilitation therapies is attributable to botulinum toxin injection. Neurologist and physical therapist interventions (47% and 48%, respectively) account for over 90% of the costs of specialists. Lastly, among concomitant drugs, approximately 60% of the costs is due to neuroleptics.

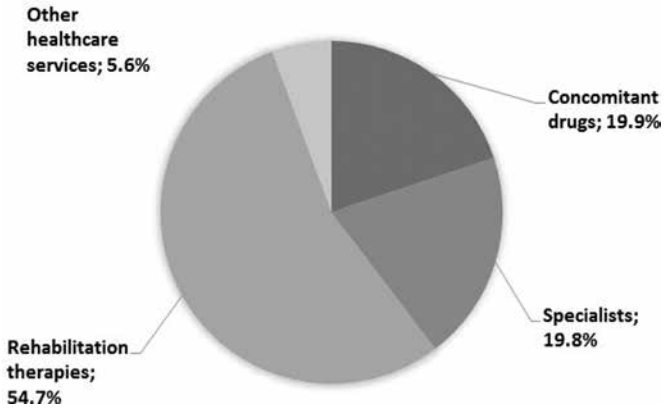

Fig. 2 - Standard cervical dystonia (CD) treatment: incidence of cost drivers.

Budget impact analysis

On the basis of epidemiological data (number of subjects with ULS or CD treated with BoNT-A), market shares (experts' estimate) and pharmacological costs of botulinum toxins (CMA estimate), we calculated the pharmacological expenditure for BoNT-As incurred by the IHNS over the five years of observation.

Tables VI and VII show the results of the analysis conducted for ULS and CD, respectively; in both cases, a comparison is carried out between two specific scenarios (Scenario A and Scenario B), differentiated solely by the considered market shares. In Scenario A (both for ULS and for CD) the market share estimated by the experts was kept constant over the observation period (ULS: Dysport® 45%, Botox® 28% and Xeomin® 27%; CD: Dysport® 39%, Botox® 28% and Xeomin® 33%), while in Scenario B the market share was changed from the second year onward by applying a Dysport® substitution effect of 6 percentage points per year, equally distributed between Botox® (minus 3 percentage points) and Xeomin® (minus 3 percentage points). During the five year period, Dysport® would rise from a 45% share in the first year to a 69% share in the fifth year in the treatment of ULS, and from 39% in the first year to 63% in the fifth year in the treatment of CD. With these trends in the market shares of Dysport® the overall reduction of the pharmaceutical expenditure incurred by the INHS over the five year period would amount to €620,428 for ULS and to €480,918 for CD (Fig. 3).

One-way sensitivity analysis

The sensitivity analysis confirmed the validity of the results of the CMA and BIA base case to changes in the main parameters considered (dose per treatment, time to next treatment and cost per vial) (Tabb. VIII and IX).

In ULS, the parameter that most influences the comparison between Dysport® and Botox® is the median dose (54% change compared to base case); in the comparison between Dysport® and Xeomin® the result is influenced in equal proportions by median dose (28% change compared to base case), median cost (21% change compared to base

TABLE VI - Budget Impact Analysis (BIA) results: ULS

	Upper limb spasticity									
BoNT-A cost	**First year**		**Second year**		**Third year**		**Fourth year**		**Fifth year**	
	No. of pts	**3,654**	**No. of pts**	**3,672**	**no. of pts**	**3,690**	**no. of pts**	**3,708**	**No. of pts**	**3,726**
	MS*	**Expenditure (€)**	**MS**	**Expenditure (€)**	**MS**	**Expenditure (€)**	**MS**	**Expenditure (€)**	**MS**	**Expenditure (€)**
Dysport® €701	45%	1,152,120	45%	1,157,765	45%	1,163,438	45%	1,169,138	45%	1,174,867
Botox® €928	28%	949,018	28%	953,668	28%	958,341	28%	963,037	28%	967,755
Xeomin® €1,031	27%	1,017,670	27%	1,022,656	27%	1,027,667	27%	1,032,702	27%	1,037,762
Scenario A	**100%**	**3,118,807**	**100%**	**3,134,089**	**100%**	**3,149,445**	**100%**	**3,164,877**	**100%**	**3,180,384**
Dysport® €701	45%	1,152,120	51%	1,312,134	57%	1,473,688	63%	1,636,794	69%	1,801,462
Botox® €928	28%	949,018	25%	851,489	22%	752,982	19%	653,489	16%	553,003
Xeomin® €1,031	27%	1,017,670	24%	909,028	21%	799,296	18%	688,468	15%	576,535
Scenario B	**100%**	**3,118,807**	**100%**	**3,072,650**	**100%**	**3,025,966**	**100%**	**2,978,751**	**100%**	**2,931,000**
Difference B-A		**0**		**-61,439**		**-123,479**		**-186,126**		**-249,384**

*Estimate provided by experts.
MS = market share; pts = patients.

TABLE VII - Budget Impact Analysis (BIA) results: CD

	Cervical dystonia									
BoNT-A cost	**First year**		**Second year**		**Third year**		**Fourth year**		**Fifth year**	
	No. of pts	**6,894**	**No. of pts**	**6,927**	**No. of pts**	**6,961**	**No. of pts**	**6,995**	**No. of pts**	**7,030**
	MS*	**Expenditure (€)**	**MS**	**Expenditure (€)**	**MS**	**Expenditure (€)**	**MS**	**Expenditure (€)**	**MS**	**Expenditure (€)**
Dysport® €669	39%	1,798,262	39%	1,807,073	39%	1,815,928	39%	1,824,825	39%	1,833,767
Botox® €748	28%	1,444,199	28%	1,451,275	28%	1,458,386	28%	1,465,532	28%	1,472,713
Xeomin® €819	33%	1,862,425	33%	1,871,550	33%	1,880,720	33%	1,889,935	33%	1,899,196
Scenario A	**100%**	**5,104,885**	**100%**	**5,129,898**	**100%**	**5,155,034**	**100%**	**5,180,292**	**100%**	**5,205,675**
Dysport® €669	39%	1,798,262	45%	2,085,085	51%	2,374,675	57%	2,667,052	63%	2,962,238
Botox® €748	28%	1,444,199	25%	1,295,781	22%	1,145,875	19%	994,468	16%	841,550
Xeomin® €819	33%	1,862,425	30%	1,701,409	27%	1,538,771	24%	1,374,498	21%	1,208,579
Scenario B	**100%**	**5,104,885**	**100%**	**5,082,275**	**100%**	**5,059,320**	**100%**	**5,036,019**	**100%**	**5,012,367**
Difference B-A		**0**		**-47,623**		**-95,713**		**-144,274**		**-193,307**

*Estimate provided by experts.
MS = market share; pts = patients.

case) and ex-factory price per vial (26% change compared to base case). For CD, in the comparison against Botox® the median dose (-76% change compared to base case) and ex-factory price (-63% change compared to base case) are the parameters that most characterize the variability of results. In the comparison against Xeomin®, the ex-factory price of vials is the only variable that significantly modifies the final result (37% change compared to base case). In the Budget Impact Analysis, the median dose is the parameter that most heavily influences the final result (ULS: 38% change; CD: -36% change).

Over the five year period, with a substitution effect of 8 percentage points, in the treatment of ULS Dysport® would reach a market share of 77%, generating an overall reduction in botulinum toxin expenditure of €0.8 million; in the treatment of CD, the market share would be approximately 71% and the reduction in toxin expenditure would amount to €650,000. With a substitution effect of 12 percentage

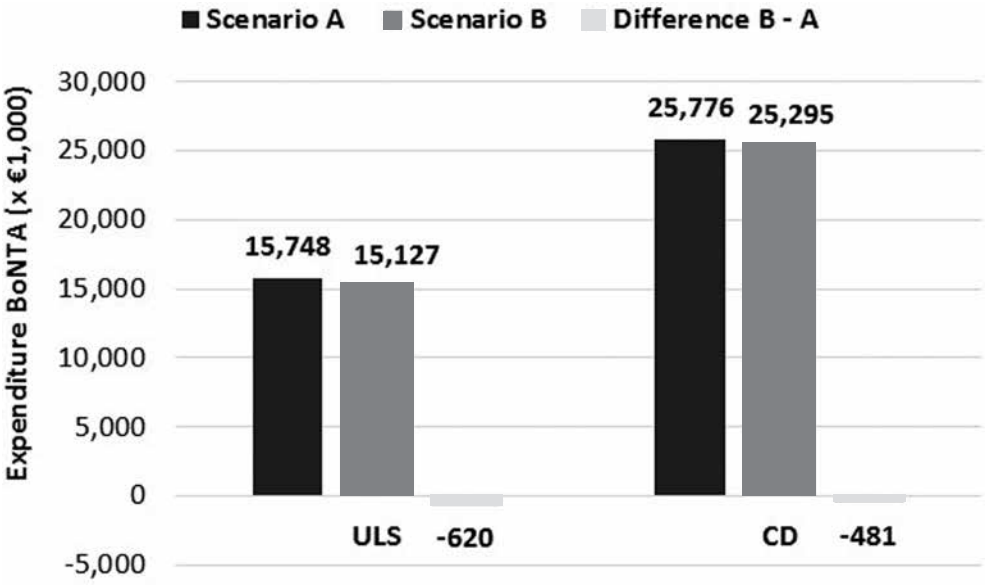

Fig. 3 - Budget Impact Analysis (BIA): results at 5 years.

TABLE VIII - Sensitivity analysis: Cost Minimization Analysis (CMA)

Difference Dysport® vs	Upper limb spasticity		Cervical dystonia	
	Botox®	Xeomin®	Botox®	Xeomin®
Base Case	**-€226.88**	**-€330.81**	**-€79.34**	**-€149.82**
Median dose	-€349.69	-€422.11	-€19.41	-€127.58
Median time to next treatment	-€215.33	-€341.47	-€68.49	-€144.31
Median cost per vial	-€242.23	-€400.59	-€90.80	-€152.05
Dose, time and median cost	-€342.22	-€492.16	-€21.32	-€124.96
Ex-factory price per vial	-€206.53	-€418.39	-€29.62	-€205.56

TABLE IX - Sensitivity analysis: Budget Impact Analysis (BIA)

Difference Scenario B vs	Upper limb spasticity	Cervical dystonia
	Scenario A	Scenario A
Base case	**-€620,428**	**-€480,918**
Median dose	-€858,542	-€308,479
Median time to next treatment	-€619,379	-€446,594
Median cost per vial	-€715,070	-€509,656
Dose, time and median cost	-€928,166	-€306,984
Ex-factory price per vial	-€695,222	-€493,558
Dysport® substitution effect		
- 8 percentage points per year	-€827,237	-€641,224
- 12 percentage points per year	-€1,240,856	-€961,836

points, in ULS the market share and the reduction in toxin expenditure would go up to 93% and €1.2 million, respectively; in CD, the expenditure reduction would be approximately €1 million, with an 87% market share.

Discussion

The results estimated by the Cost Minimization Analysis indicate Dysport® to be the cost-saving alternative in the treatment of upper limb spasticity and cervical dystonia compared to Botox® (ULS: -€226.88; CD: -79.34) and Xeomin® (ULS: -€330.81; CD: -149,82). At national level (Budget Impact Analysis), these differences in cost could result in a reduction in pharmaceutical expenditure for botulinum toxins, which would be more or less significant depending on the level of use (substitution rate) of Dysport® compared to the other two BoNT-As.

As the calculation of the average cost per treated patient is based solely on a data collection process that involved 12 experts, it was in our opinion extremely important to verify, first and foremost, whether the cost estimated in this document were comparable with those of other studies. Weighting the average costs of treatment of the three BoNT-As by the respective market shares, we calculated an average annual cost per patient treated with botulinum toxin plus standard therapy of €1,993.08 for upper limb spasticity and of €1,425.44 for cervical dystonia.

The decision to involve a group of experts was prompted by the need to estimate the average doses of the main botulinum

toxins type A in the treatment of ULS and CD, and to ensure that such doses actually reflected Italian clinical practice, as the information available in the literature is conflicting and therefore not useful in determining a reliable average cost of treatment. To ensure that the clinical practice criterion was met as closely as possible, each expert was asked to consider for both indications the data of the last 10 patients, in chronological order, who had been referred to the centre and treated with Dysport®, Botox® or Xeomin®, for a total of 30 subjects for each of the two indications. For each patient thus identified, they were asked to consider, in chronological order, the doses of the last two treatments, for a total of 20 dose measurements (two per patient) for each of the toxins considered. The average dose per type of toxin (Dysport®, Botox® and Xeomin®) and therapeutic indication (ULS or CD) indicated by the expert was then calculated as an average of the 20 corresponding dosages.

For the purpose of evaluating the uncertainty of the key parameters that determined the results of the base case, an in-depth sensitivity analysis was conducted on the dose per treatment, the time to next treatment and the average cost per vial. In all the individual comparisons conducted by the one-way sensitivity analysis or the multivariate analysis, Dysport® always determined the lowest average cost of treatment compared to Botox® and Xeomin®.

In terms of therapeutic indication, upper limb spasticity was found to involve a smaller average number of treatments (3.5) compared to cervical dystonia (4.2), while in terms of botulinum toxins Dysport® determines a slightly smaller number of administrations compared to the other toxins (ULS: Dysport® 3.4, Botox® 3.5 and Xeomin® 3.6; CD: Dysport® 4.1, Botox® 4.2 and Xeomin® 4.3).

A possible limit of the CMA could be the fact that the healthcare consumptions of standard therapy are not distinguished by specific toxin administered. This choice is justified by the considerations set out below. As differences between botulinum toxins seem to be attributable to dose rather than to their inherent safety and the toxin's ability to achieve therapeutic response (5, 8-11, 17-20), in our opinion it was reasonable to assume that no difference in efficacy and safety profiles corresponds to no difference in consumptions, and therefore in the costs determined by the standard therapy combined with the three compared botulinum toxins. Moreover, the main objective of the CMA was to estimate the differences, if any, in the costs of treatment of the BoNT-As, attributable mainly to the different doses used to achieve the therapeutic target.

There are differences in consumption and cost for the standard therapy used in ULS or CD. In ULS, the standard therapy accounts for approximately 57% of the total costs, with a higher use of specialist interventions, whereas in CD it accounts for 48% of the total costs, with a higher use of rehabilitation therapies.

The results of the budget impact analysis should also be read in light of certain observations referring to the epidemiological data used to build the cohorts of patients treated with BoNT-A and the substitution rates assumed for Dysport®. In the first case, data from the literature were used when available; alternatively, estimates provided by specific market surveys were used. As partial justification of possible estimating errors, it should be noted that any cohorts of patients larger or smaller than those adopted in the base case would essentially have increased or reduced, but not eliminated, the economic advantage deriving from a greater use of Dysport® compared to its competitors. In the second case, i.e. with reference to Dysport® substitution rates, as no real rates are available, a rate of 6% was assumed in the base case, which was then changed in the sensitivity analysis. Here again, it is important to point out that Dysport® substitution rate selected, it would result, in the long term (five years) in a reduction in the pharmaceutical expenditure determined by the three BoNT-As.

Conclusions

The result of the Cost Minimization Analysis has shown that Dysport® is the cost-saving therapeutic option, when compared in the INHS perspective against Botox® or Xeomin® in the treatment of both upper limb spasticity and cervical dystonia.

While recognizing the potential limits in determining the number of patients treated with botulinum toxins and the respective market shares, the subsequent Budget Impact Analysis suggests that an increase in patients treated with Dysport® would lead to a reduction in the pharmaceutical expenditure for BoNT-As incurred by the INHS. Therefore, a choice in favour of Dysport® could represent an efficient allocation of healthcare resources.

Disclosures

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