Budget impact of botulinum toxin treatment for spasticity after stroke — a German perspective

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Received: 22 February 2019 / Accepted: 25 October 2019 / Published online: 28 November 2019
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Abstract

Aim Botulinum toxin agents can improve the quality of life of patients with post-stroke upper limb spasticity (ULS) and are recommended by international and German guidelines. However, health-services research indicates an underuse of botulinum toxin agents in this patient group. The study aims to clarify the budget impact of treatment with botulinum toxin agents according to the guidelines for all eligible patients with ULS in Germany compared to usual care.

Methods The budgetary impact for the statutory health insurance system was estimated by calculating a Markov cohort model with a timeframe of 5 years comparing three treatment options. Four health states were included. The base-case analysis compares standard doses of two botulinum toxin agents to usual care. The model accounts for direct medical costs. Sensitivity analyses vary doses of botulinum toxin agents and prevalence of spasticity after stroke.

Results In the base case, both botulinum toxin agents lead to increased costs compared to usual care. Treatment with Dysport® (cumulative costs for the 5-year period: €280,321,317) is less expensive than the treatment with Xeomin® (€377,511,529). Cumulative costs over 5 years in usual care are €61,306,062.

Conclusion The botulinum toxin therapy is associated with additional costs, but an increased use of botulinum toxin would be consistent with guideline-based therapy. In particular, it has to be considered that spasticity as a chronic condition is accompanied by a relevant loss of quality of life. Thus, considering only the therapy costs may not be sufficient for making final therapeutic decisions.

Keywords Botulinum toxin · Spasticity · Germany · Budget impact analysis

Introduction

About 39% of post-stroke patients suffer from long-term disabilities (Luengo-Fernandez et al. 2013). Spasticity is one of the causes of these disabilities, often presenting as an upper limb spasticity (ULS) (Watkins et al. 2002). Patients with ULS are unable to control the initiation of muscle reflexes of the upper limb, resulting in impaired function, reduced active movement, and distressing limb postures (Abogunrin et al. 2015; Gracies

et al. 2015). Moreover, spasticity can cause severe problems such as painful limb deformities, decubitus ulcers, or osteoporosis. Therefore, ULS results in tremendous impairment to the daily living activities of the patient (Graham 2013).

There is no cure for ULS, although several treatment options are available to improve quality of life. In Germany, these options include various physical therapies (muscle lengthening, splinting, electrical stimulation), ergotherapy or oral medications (baclofen, diazepam, tizanidine, etc.) and chemodenervation with botulinum toxin (Platz et al. 2018; Wissel et al. 2011). Oral medications reduce spastic muscle tone, although often a dosage in the upper range is necessary, which increases the risk of adverse events in the group of patients with ULS, for example the weakening of functionally relevant muscles (Platz et al. 2018). The use of botulinum toxin in the treatment of patients with ULS is recommended by the German guidelines. Several controlled trials and meta-analyses (Platz et al. 2018) reveal a dose-dependent reduction of spastic muscle tone, and an improvement in passive

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mobility and functioning of affected joints. Especially in focal spasticity, the risk–benefit balance of treatment with botulinum toxin is superior to that of oral antispasmodic agents (Platz et al. 2018). The German guidelines recommend the injection of botulinum toxin due to its effectiveness and fewer side-effects compared to oral medication (Platz et al. 2018; Wissel et al. 2011).

Information on the implementation of botulinum toxin as a treatment option for ULS patients in Germany is sparse. Studies indicate an undersupply (Dressler et al. 2015; Jost et al. 2015; Kerkemeyer et al. 2017; Potempa et al. 2019; Wissel et al. 2016). A recently published survey analyses the standard of care for patients with spastic movement disorder among general practitioners in Germany (Potempa et al. 2019). In the majority of cases (92.7%), spastic movement disorder has been caused by stroke. Study results indicate that treatment might not be in accordance with guidelines in several cases, as half of the interviewed general practitioners reported prescribing oral antispasmodic medication in more than 80% of their patients with spastic movement disorder. Only less than 10% of the patients are being treated with botulinum toxin. A survey including 800 practicing neurologists in Germany reveals that most of the neurologists in Germany, who answered the survey, reported barriers with regard to the use of botulinum toxin (Kerkemeyer et al. 2017).

A budget impact model for the United Kingdom (UK) indicates a cost reduction in terms of the implementation of botulinum toxin as an additional treatment option compared to standard treatment for patients with ULS, due to reduced resource use (Abogunrin et al. 2015). The budgetary impact of a widespread use of botulinum toxin in all eligible patients with ULS after stroke has not been assessed for the German healthcare system yet.

The aim of this study is to examine the economic impact for the German healthcare system if there were a more widespread use of the treatment with botulinum toxin for patients with spasticity after stroke.

Methods

Based on the budget impact analysis method, a Markov model was developed to analyze the budgetary effects of an increased application of botulinum toxin in patients with spasticity after stroke, compared to the rare application of botulinum toxin in usual care. With regard to the treatment of spasticity in Germany, the budgetary impact for the statutory health insurance includes only direct costs — which refers to medical costs based on health services such as outpatient and inpatient treatment. A Markov cohort model was calculated in Microsoft EXCEL®. Considering the two currently approved botulinum toxin agents in Germany, three different strategies were

included: two for the agents AbobotulinumtoxinA (Dysport®) and IncobotulinumtoxinA (Xeomin®) and one for usual care with oral medication (oral baclofen, tizanidine, benzhexol/trihexyphenidyl). Patients in all strategies received physiotherapy and outpatient medical care over the modeling horizon.

The Markov cohort model was developed with a cycle length of 1 year. The budget impact was calculated for 5 years starting with the base year of 2013. Discounting was integrated at a 3 % rate according to German practice.

Model structure

The model includes four health states: “health”, “stroke”, “upper limb spasticity” as a result of a stroke, and “death”. Figure 1 shows the health states throughout the modeling horizon. Patients can change health state along the arrows in each cycle. Development of ULS was taken into account within the first year after stroke only. Since there is no cure for spasticity, patients are not able to move back to the healthy state. Patients with lower limb spasticity are not considered in the model.

Epidemiological data

All input parameters were derived from literature search. The Markov cohort consists of the German population 25 years and older with spasticity after stroke (Statistisches Bundesamt (Destatis) 2013a). Data for the annual probability of stroke was identified from a German patient registry (Kolominsky-Rabas et al. 1998). Based on the incidence of stroke derived from Kolominsky-Rabas et al. (1998) we estimated the number of strokes in the German population. The prevalence of spasticity after stroke was estimated for a mean value of 27.5% (Lundström et al. 2008; Watkins et al. 2002). It was assumed that at least half of the patients with spasticity after stroke have lower limb spasticity and half of the patients have ULS (Urban

Fig. 1 Markov transition model

et al. 2010). Additionally it was assumed that 38% of these patients with ULS are suitable for treatment with botulinum toxin (Ward et al. 2005). In summary, a proportion of 20% of patients with spasticity after stroke — those who suffer from ULS and are suitable for therapy with botulinum toxin — were included in the model. Mortality after stroke was assumed to be 32% for women and 24% for men (Bronnum-Hansen et al. 2001). Compared to the healthy population in subsequent years, a higher mortality was applied. To model those higher rates in the first year and subsequent years after stroke, the standardized mortality ratios reported by Bronnum-Hansen et al. (2001) and the overall mortality rates for each age group were considered (Statistisches Bundesamt (Destatis) 2013b). Table 1 presents the number of patients entering the cohort each year. The calculation is based on the new cases of spasticity each year and the mortality per year.

Resource use

In the base-case analysis, the standard doses of the two botulinum toxin agents are compared to usual care. According to the medicinal product's professional information, the highest recommended doses are 1500 units for Dysport and 500 units for Xeomin. Because in routine care treatment doses seem to vary substantially from pharmaceutical information, a dose of 1000 units for Dysport® (Gracies et al. 2015) and 400 units for Xeomin® was assumed as standard doses (Elovic et al. 2016; Kanovsky et al. 2011; Kanovsky et al. 2009) (Table 2). In the base-case analysis, the standard doses were applied; in sensitivity analysis, the highest doses were applied.

The use of further medication differs between patients treated with botulinum toxin and those in usual care (Ward et al. 2005). While 45.6% of patients in usual care received baclofen, only 16.9% were treated with it in the botulinum toxin group. In the latter group, 1.3% received benzhexol/trihexyphenidyl and none received tizanidine. In usual care, 4.4% were treated with benzhexol/trihexyphenidyl and 1.7% with tizanidine. For oral medication, daily doses recommended in the professional information for the medicinal products were applied: 75 mg for oral baclofen, 24 mg for tizanidine, and 16 mg for benzhexol/trihexyphenidyl.

Further direct costs were treatment costs in terms of contacts to neurologists, physiotherapists, and primary care physicians, as well as costs for hospitalization and the use of splints to prevent contractures. All data on resource use were derived from studies, except for the number of neurologist visits for the treatment with botulinum toxin (Shackley et al. 2012; Shaw et al. 2010; Ward et al. 2005). In Germany, the injection of botulinum toxin agents has to be performed by a neurologist once per quarter of the year. Therefore, the number of visits was assumed to be four contacts per year. Table 3 shows the resource use in both strategies per year.

Cost data

Costs were calculated from the perspective of the German statutory health insurance system. Social costs such as productivity loss are not considered. In the model, costs for the cohort are evaluated for a 5-year horizon.

The cost analysis includes outpatient and inpatient costs. Outpatient costs such as physician contacts and drug prescriptions are obtained from Bock et al. (2015) and from the LAUER-TAXE® (2017), a German register for pharmaceutical drugs. For each drug prescription the biggest package size was assumed. Inpatient costs were calculated by the number of days of hospitalization multiplied by the costs per day of hospitalization from Bock et al. (2015) (Table 4). The costs for medical therapy per year and strategy for the base case are shown in Table 5. All cost data are expressed in Euro, using 2013 as reference year. Costs were adjusted to the year based on the German harmonized consumer price index, which provides a comparable measure of inflation and price stability in European countries (Statistisches Bundesamt (Destatis) 2017).

Direct costs resulting from inpatient and outpatient consultations indicate that hospitalization costs are a main cost driver in usual care, at €452. In addition to medication, in the botulinum toxin group most of the costs are incurred for neurologists (€179) and hospitalization (€125). The highest annual costs for a botulinum toxin agent are €4479 for Xeomin®, the lowest €3209 for Dysport®. The therapy with oral baclofen with €161 presents the highest costs for medical treatment in usual care (Table 5).

Table 1 Number of patients with ULS and suitable for treatment with botulinum toxin agents in the cohort per year

Number of patients	Year of the cohort				
	2013	2014	2015	2016	2017
New cases of spasticity in the year	40,004	40,786	42,336	43,813	45,004
Deaths	9989	12,808	16,032	19,159	22,157
Cases of spasticity (cumulative)	40,004	80,789	123,125	166,938	211,942
Cases with ULS with indication to treatment (cumulative)	8001	16,158	24,625	33,388	42,388

ULS: upper limb spasticity

Table 2 Doses of botulinum toxin agents

Active pharmaceutical ingredient	Trade name	Units		Sources
		Dose base case	Highest dose	
AbobotulinumtoxinA	Dysport®	1000	1500	Gracies et al. 2015; Wissel et al. 2011
IncobotulinumtoxinA	Xeomin®	400	500	Elovic et al. 2016; Kanovsky et al. 2011; Kanovsky et al. 2009; Wissel et al. 2011

Sensitivity analyses

Sensitivity analyses were conducted to account for uncertainty. Relevant parameters of the model were varied and the impact on overall results was assessed. Sensitivity analyses especially consider dosage of botulinum toxin (Table 2, highest dose) and a variation of the prevalence.

Results

The model describes a time frame of 5 years treating patients with ULS after stroke and including new cases into the model. Starting with the treatment of 8001 patients with ULS in 2013, the model includes 42,388 patients with ULS in 2017 (Table 1). Three strategies are being compared for the German healthcare situation: a) usual care, b) a widespread use of Dysport®, and c) a widespread use of Xeomin®.

During the 5-year period, direct medical costs for usual care are about €61,306,000 (Table 6). The strategies with a wide-spread use of botulinum toxin compared to usual care indicates additional costs for the German statutory health insurance. Using Dysport®, the cumulated overall costs are about €280,321,000. Therefore, compared to usual care, there is an increase of about €219,015,000 for the use of Dysport®. The use of Xeomin®, with overall costs of about €377,512,000 for the period of 5 years, displays about €316,205,000 higher costs compared to usual care (Table 6).

Increasing the dose to a maximum according to Table 2, the overall costs for the botulinum toxin drugs increase to

€403,079,000 for Dysport® and €463,188,000 for Xeomin® (sensitivity analysis). In this sensitivity analysis, costs for the use of botulinum toxin agents compared to the usual care amount up to €341,773,000 for Dysport® and €401,882,000 for Xeomin®. This sensitivity analysis shows increased costs for all botulinum toxin agents compared to usual care (Table 7). Dose variations are strongly associated with costs.

By varying the prevalence of spasticity after stroke to a minimum of 17% and a maximum of 38% the costs over 5 years for all botulinum toxin drugs decrease and increase, respectively (Table 8).

Varying the discounting rate from 3 % to 0 % or 5 % results in slightly different total costs but does not affect the direction of the findings (data not shown).

Calculating with actual cost data for pharmaceutical drugs, accumulated costs for Dysport® and usual care are constant. Due to shifting package sizes the average package costs for Xeomin® have increased, which leads to additional costs of €354,365,824 compared to usual care.

Discussion

This analysis shows the budget impact for an increased use of the botulinum toxin agents AbobotulinumtoxinA (Dysport®) in standard dosage of 1000 units or IncobotulinumtoxinA (Xeomin®) in standard dosage of 400 units compared to usual care in patients with ULS from the perspective of the German statutory health insurance system. Both botulinum toxin agents incur additional costs. This is in contrast to the findings

Table 3 Resource use per year and patient

Resource use	Botulinum toxin	Usual care	Source
Visits			
Neurologist	4.00	1.90	(Ward et al. 2005)*
Physiotherapist	3.69	3.48	(Shackley et al. 2012)‡
Primary care physician	0.85	0.59	(Shackley et al. 2012)‡
Days of hospitalization	0.23	0.83	(Shackley et al. 2012)‡
Splint	0.23	0.29	(Shaw et al. 2010)

*Number of neurologist visits in usual care are extracted from this publication

‡ Calculation of mean number of contacts related to the complete study population

Table 4 Costs for resource utilization per year and patient

Costs for resource use	Botulinum toxin	Usual care
Neurologist	€178.65	€84.86
Physiotherapist	€59.43	€56.03
Primary care physician	€17.05	€11.89
Hospitalization	€125.23	€452.06
Splint	€9.81	€12.19
Total costs	€390.17	€617.03

of Abogunrin et al. (2015), who determined all kinds of botulinum toxin to be cheaper than the best supportive care in patients with ULS after stroke, although treating a patient with IncobotulinumtoxinA costs more per patient annually than with AbobotulinumtoxinA. The reason for these differences are the lower medication costs in the model of Abogunrin et al. (2015). The calculation of the model underlying this publication with similar prices per unit in the budget impact of a treatment with AbobotulinumtoxinA (Dysport®) declines to about €138,000,000.

Sensitivity analysis with maximal doses of botulinum toxin agents indicates increasing the treatment costs compared to usual care. In addition, the sensitivity analyses have shown a strong influence of the assumed prevalence of spasticity on total costs, which is consistent with the interpretation of Abogunrin et al. (2015). The model includes input parameters on the prevalence of spasticity after stroke from studies of the USA and Sweden (Lundström et al. 2008; Watkins et al. 2002). Data from a German study indicating a prevalence of 10% were not included, due to the fact that these data did not fit within the wide range of international studies (18% to 42%) (Egen-Lappe et al. 2013).

The current study has some limitations. Epidemiological data on spasticity are sparse, as well as on treatment and resource use. Therefore, we had to make several assumptions. To get more valid data for the context of the German healthcare system, especially for the prevalence of patients with ULS after stroke suitable for treatment with botulinum toxin agents, further studies, e.g., with health insurance fund data are needed.

Table 5 Medication costs per year and patient

Strategy	Botulinum toxin	Usual care
Dysport®	€3208.68	–
Xeomin®	€4478.88	–
Oral baclofen	€59.71	€161.12
Tizanidine	€0.00	€6.12
Benzhexol/trihexyphenidyl	€5.01	€16.94
Total costs	Dysport: €3273.40 Xeomin: €4543.60	€184.18

Table 6 Costs for botulinum toxin agents compared to usual care (5 years)

Strategy	Costs over 5 years	Difference compared to usual care
Base case		
Dysport®	€280,321,317	€219,015,255
Xeomin®	€377,511,529	€316,205,467
Usual care	€61,306,062	

Because of a lack of data on the applied doses of botulinum toxin agents, actual costs in terms of the botulinum toxin therapy are afflicted with uncertainty. Data for the dose of Dysport® is derived from a randomized controlled study, which was conducted on 243 patients in 34 centers in nine countries (Gracies et al. 2015). Patients receive 500 or 1000 units of Dysport®. In the base case, a dose of 1000 units was assumed. The dose of Xeomin® in the base case is based on a double-blind study including 145 patients from 23 sites in three European countries (Czech Republic, Hungary and Poland) (Kanovsky et al. 2011). The same dose was applied in a randomized controlled study with 317 patients (Elovic et al. 2016). The transferability of these data to the German healthcare setting is also afflicted with uncertainty. Additionally, costs due to other healthcare and social services resource use are not included. Shackley et al. (2012) show that these costs are much higher in patients without botulinum toxin therapy, which potentially induces an underestimation in terms of the difference in costs between the use versus the renunciation of botulinum toxin use.

A lack of data was identified in terms of long-term care. It may be assumed that therapy with botulinum toxin has a positive impact on the need of care due to avoidance of contractions. Performing a systematic literature search, we could not find any publications focusing on this aspect. For this reason, we did not include costs of long-term care.

The 2019-updated German guideline on the treatment of the spastic syndrome recommends the use of botulinum toxin (Platz et al. 2018). There is a positive effect on the ULS, and

Table 7 Sensitivity analysis with maximal doses of botulinum toxin agents (5 years)

Strategy	Costs over 5 years	Difference compared to usual care
Highest dose		
Dysport®	€403,079,016	€341,772,954
Xeomin®	€463,187,931	€401,881,869
Usual care	€61,306,062	

Table 8 Sensitivity analysis with lowest and highest prevalence of spasticity after stroke (5 years)

Strategy	Costs over 5 years	Difference compared to usual care
Prevalence of spasticity 17%		
Dysport®	€173,436,897	€135,506,378
Xeomin®	€233,569,209	€195,638,689
Usual care	€37,930,519	
Prevalence of spasticity 38%		
Dysport®	€387,024,211	€302,382,306
Xeomin®	€521,209,385	€436,567,481
Usual care	€84,641,905	

thus an improved integration of the spastic paralyzed arm in everyday life. Botulinum toxin therapy seems to have a better benefit–risk balance, and should be preferred to the sole use of oral antispastics. As calculated in the model, the additional use of oral antispastics in low, side-effects-free dosage can be considered. However, a study by Potempa et al. (2019) indicates — despite the recommendation in the guidelines — only a minor use of botulinum toxin in the treatment of patients with spasticity in Germany. The reasons for non-treatment with botulinum toxin include missing therapists as well as insufficient reimbursement of costs by the social health insurance system.

As shown by Potempa et al. (2019), baclofen is the most commonly used among oral antispastic drugs in Germany. However, this drug is mentioned on the Priscus list, an overview of potentially inadequate medication for elderly patients (Holt et al. 2011). Considering that patients who experience post-stroke spasticity are likely to be older, therapy with botulinum toxin as recommended in the German guideline may support less frequent use of oral antispastics such as baclofen.

An alternative approach to analyzing the impact of treatment with botulinum toxin agents including patient-relevant outcomes would be to conduct a cost-effectiveness study. In such a cost-effectiveness study performed in a similar setting, the incremental cost per quality adjusted life year (QALY) for patients with post-stroke ULS could be estimated (Shackley et al. 2012).

In this budget impact analysis, the economic effects of an increased use of botulinum toxin agents for patients with ULS are determined from the perspective of the German statutory health insurance system. Although the botulinum toxin therapy, as shown in the model, is associated with additional costs, the increased use of botulinum toxin would be in line with the guideline-based therapy. In particular, it has to be considered that spasticity as a chronic condition is accompanied by a relevant loss of quality of life, so considering only the therapy costs may not be sufficient for a final decision. Patient-relevant outcomes should also be taken into account.

This study reveals a common finding in economic evaluation that an improvement in medical outcomes goes along with additional costs. In the end, a social debate is necessary to decide if the benefits justify the costs.

Funding information This study was funded by Ipsen Pharma GmbH.

Compliance with ethical standards

Conflict of interest Alexander Wilke is employed at Ipsen Pharma GmbH.

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