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Long-Term Efficacy and Safety of IncobotulinumtoxinA (Xeomin®) and Conventional Treatment of Poststroke Arm Spasticity

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ABSTRACT

Objective: To compare efficacy and safety of incobotulinumtoxinA (INCO) to conventional antispastic therapy (CON) for poststroke arm spasticity in routine clinical practice over a 1-year period.

Design: Prospective, non-interventional, open-label, parallel-group study.

Setting: Forty-seven centres in Germany.

Participants: Patients with poststroke arm spasticity, 108 included in INCO, 110 in CON.

Intervention: CON: conventional antispastic treatment including oral antispastic medications, physiotherapy and occupational therapy; INCO: 3-monthly incobotulinumtoxinA injections plus conventional therapy if required.

Main outcome measures: Changes over the 1-year treatment period in muscle tone (Ashworth Scale), functional disability (Disability Assessment Scale, DAS), and quality of life (SF-12 Health Survey). Therapy outcome was rated with the Goal Attainment Scale (GAS), efficacy and tolerability of treatment with the Global Clinical Impression Scale.

Results: Muscle tone improved for all spasticity patterns with Ashworth Scale responder rates between 63%- 86% (INCO) and 16%-27% (CON). Median improvement in functional disability was -1.0 (INCO) and 0.0 (CON) for all DAS domains. Ninety-three percent in INCO and 30% in CON attained their goals on the GAS. Efficacy was rated as good and very good in 93% (physicians) and 90% (patients) in INCO, in CON figures were 36% and 37%. Tolerability was rated as good and very good in 99% (physicians) and 99% (patients) in INCO, in CON 76% and 66% respectively. Quality of life improved by 8.0 (physical score) and 10.8 (mental score) in INCO, in CON by 0.8 and 5.7, respectively.

Conclusions: IncobotulinumtoxinA combined with rehabilitation and oral medication produces a much more robust improvement in all aspects of arm spasticity than conventional antispastic treatment. Effects are stable over a period of 1 year, adverse effects are negligible. IncobotulinumtoxinA should be considered treatment of choice for poststroke arm spasticity.

Strengths and limitations of this study

- This is the largest study of its kind carried out in Germany.
- There is a potential bias because of the 100% participation of specialist physicians in the incobotulinumtoxinA arm compared to only 11% in the conventional therapy arm: their greater expertise in the treatment of spasticity compared to general practitioners provided more patients with additional physical therapeutic measures which might have increased the benefits of botulinum toxin treatment.
- The non-interventional study design reflects the real-world health care situation in Germany in the treatment of poststroke spasticity.

INTRODUCTION

Spasticity is a common complication of motor stroke. It is often more pronounced in arm than in leg muscles and occurs in approximately 30% of patients suffering from motor stroke.[1] Patients with poststroke spasticity often experience marked functional impairments which may result in restrictions in their daily routine, in dependence on assistance from family and/or caregivers and in impaired social participation.[2] This may lead to loss of self-esteem, poor body image, depression and a diminished quality of life. Conventional treatment options are numerous, efficacy, however, is limited. For adult upper limb spasticity, the use of botulinum toxin (BT) therapy is supported by various guidelines, expert opinions and a recent evidence-based review.[2-6] However, BT therapy for spasticity has so far not been implemented in routine health care practice.[1, 7]

We wanted to study efficacy and safety of BT therapy and of conventional antispastic treatment in patients with poststroke arm spasticity in routine clinical practice in Germany over a 1-year period.

METHODS

Study Design

This study was based on a prospective, non-interventional, open-label, multicentre, parallel-group design. In CON, patients received conventional antispastic treatment including oral antispastic medications, physiotherapy and occupational therapy at the physician's discretion. In INCO, patients received incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, Frankfurt/M, Germany [8]) and additionally conventional treatment, if required. Prior to initiation of the study, physicians had to choose participation in the CON or INCO treatment arm. All treatment decisions were made before inclusion of the patient in the study. IncobotulinumtoxinA was applied according to the physician's decision with respect to dose and muscles injected. Antispastic treatment was documented. Participating physicians were

asked to document the first four eligible patients presenting at their practice using standardised report forms. Up to 16 patients could be included per site.

The patient flow in this study is shown in figure 1. At baseline visit (V1), all patients were prescribed their respective antispastic treatment and INCO patients received their first incobotulinumtoxinA injections. Patients then presented every three months for follow-ups at visits V2 (month 3), V3 (month 6), V4 (month 9) and V5 (month 12) when INCO patients received their subsequent incobotulinumtoxinA injections. To document maximum incobotulinumtoxinA efficacy, INCO patients were additionally evaluated 4 weeks after V1, V3 and V5, respectively, at V1b, V3b and V5b.

The study was approved by the ethics committee of Hannover Medical School and conducted by the Institute of Empirical Health Economics, Burscheid, Germany at 47 centres in Germany between April 2012 and May 2014 in accordance with section 4, subsection 23 and section 67, subsection 6 of the Medicinal Products Act of the Federal Republic of Germany. All participating patients gave written informed consent.

Patients

Inclusion criteria included diagnosis of poststroke arm spasticity, indication for antispastic treatment, adult age, ability to read and to understand the study information material and to complete the patient questionnaire. Exclusion criteria included simultaneous participation in another spasticity trial, application of BT less than 12 weeks before inclusion in this study, hypersensitivity to BT drugs or their individual contents, infection at the intended injection site and presence of neuromuscular disorders such as myasthenia gravis and Lambert-Eaton syndrome.

Parameters

As primary assessment parameter, changes in muscle tone was evaluated with a responder analysis for all clinical patterns of upper limb spasticity. Muscle tone was evaluated with the *Ashworth Scale* (AS; Grade 0: no increase in muscle tone; Grade 1: slight increase in muscle tone, giving a catch when the affected limb is moved in flexion or extension; Grade 2: more marked increase in muscle tone, but limb easily flexed; Grade 3: considerable increase in muscle tone, passive movement difficult; Grade 4: limb rigid in flexion or extension).[9] A reduction by at least one point was considered clinically meaningful. Patients with a clinically meaningful response were considered responders.

Functional disability was rated by the *Disability Assessment Scale* (DAS) for the four domains hygiene, getting dressed, limb position and pain (Grade 0: no disability; Grade 1: mild disability; Grade 2: moderate disability; Grade 3: severe disability).[10] A reduction by at least one point was considered clinically meaningful.

Therapy outcome was documented by a simplified version of the *Goal Attainment Scale* (GAS).[11] During each visit, patients and physicians chose three treatment goals (priority rating 1, 2, and 3) they wanted to attain over the next three months from a list of 17 items. For documentation, physicians only documented if the treatment goal was attained or not. The list of goals is shown in table 1.

Table 1: List of treatment goals. At each visit patients chose three treatment goals they wanted to attain until the next visit.

Pain relief
Reduction of frequency of muscle spasms
Reduction of involuntary movements
Improvement of dexterity
Improvement of self care: personal hygiene

Improvement of self-care: eating
Improvement of sexual activity
Prevention of contractures and deformation
Improvement of self care: hand hygiene
Improved body image
Improved fit of clothing
Facilitation of rehabilitation
Reduction of use of systemic medication in antispasticity treatment
Reduction of daily care measures
Reduction of care measures regarding movements
Easier application of (arm) splints and extended usage
Reduction/prevention of surgical interventions

Global Clinical Impression (GCI) of effectiveness and tolerability of the respective treatment was rated by patients and physicians separately at the end of the observation period as very good, good, satisfactory, poor, or very poor.

Quality of life was rated by the patients with the *SF-12v2 Health Survey,* a shorter version of the SF-36 Health Survey.[12] The 12 SF-12 Health Survey items are subsumed under the dimensions 'mental health' and 'physical health'. Possible scores in both domains range from 0 to 100, higher scores indicating a higher quality of life.

To assess safety, physicians monitored the occurrence of *adverse events* (AE) and *serious adverse events* (SAE) during the entire 1-year observation period.

Statistical Analysis

Documented data were processed with single data entry using Oracle Database Online Documentation 11g Release 2 (Oracle, Redwood Shores, CA, USA). All data were checked

for completeness, consistency and plausibility. The efficacy analysis included all patients in INCO or CON for at least three months. Except for the primary parameter, all analyses were descriptive and exploratory. Missing data were not imputed. End of observation time point was V5 for CON and V5b for INCO. The primary study parameter (changes in AS) was evaluated with a responder analysis for all clinical patterns of upper limb spasticity. All patients with baseline AS ≥1 were included in the respective analysis. Treatment response was defined as AS improvement ≥1 from baseline to end of the observation period. Fisher's exact test was used for comparison of treatment response between INCO and CON. The influence on treatment response regarding the independent variables gender, height, weight, body mass index, age, time since stroke, duration of spasticity, treatment arm and baseline AS (for the investigated clinical patterns) was tested using logistic regression analyses. P values for DAS changes over the course of the study were calculated with the Wilcoxon-Mann-Whitney test. SF-12 Health Survey changes were evaluated using the physical and the mental component score. Scores were calculated using a fixed algorithm and were based on the analysis manual of the German norm from 1994.[13] Comparisons of SF-12 Health Survey scores between baseline and end of observation employed the paired t-test. All patients receiving antispastic treatment at least once during the observation period were included in the tolerability analysis. AEs were encoded with the Medical Dictionary for Regulatory Activities version 13.0 (MedDRA). The Chi-square test was used to compare AE incidences between the treatment arms.

RESULTS

Demographics

Table 2 summarises the baseline characteristics of the two study groups; 108 patients were included in INCO at 21 study sites, 110 patients in CON at 26 study sites.

Table 2: Demographic and baseline characteristics of the study population at V1.

	INCO (n=108)	CON (n=110)
Male gender [n]	58 (53.7%)	70 (63.6%)
Female gender [n]	50 (46.3%)	40 (36.4%)
Age [years]	61.7±12.9	67.8±12.7
Body mass index [kg/m^2]	26.7±4.1	27.7±4.8
Time since stroke [years]	7.5±5.8	5.3±5.1
Type of stroke		
ischemic	51 (47.2%)	43 (39.1%)
haemorrhagic	16 (14.8%)	7 (6.4%)
others	21 (19.4%)	29 (26.4%)
no data	20 (18.5%)	31 (28.2%)
Duration of upper limb spasticity [years]	6.6±6.3	4.9±5.4
Previous antispastic medication [n]	85 (78.7%)	65 (59.1%)
Previous botulinum toxin therapy [n]	67 (62%)	0

Data are mean ± standard deviation or number of patients (%). INCO, patients receiving incobotulinumtoxinA; CON, patients receiving conventional therapy.

Eighty-nine percent of the patients completed the observation period. Fifty-seven percent of all patients presented with combined arm and leg spasticity; 54% (INCO) and 32% (CON) had arm spasticity only. The most frequent clinical spasticity patterns were flexed elbow (86%), flexed wrist (72%), shoulder adduction/internal rotation (71%), clenched fist (71%) and forearm pronation (71%). As shown in table 2, INCO patients had suffered from

spasticity for a longer period of time with a higher proportion of patients with AS ≥2 in most of the clinical patterns at baseline than CON patients (table 3).

Table 3: Clinical patterns of arm spasticity in patients with a baseline severity in Ashworth score ≥2 at V1.

	INCO (n=108)	**CON (n=110)**
Flexed elbow	91 (84.3%)	59 (53.6%)
Clenched fist	77 (71.3%)	40 (36.4%)
Flexed wrist	67 (62.1%)	58 (52.7%)
Pronated forearm	63 (58.3%)	49 (44.6%)
Thumb-in-palm	53 (49.1%)	43 (39.1%)
Shoulder adduction and internal arm rotation	52 (48.2%)	40 (36.3%)
Shoulder abduction	36 (33.3%)	45 (40.9%)
Shoulder elevation	32 (29.6%)	46 (41.8%)
Intrinsic plus hand	20 (18.5%)	33 (30.0%)

Data are number of patients (%). Multiple responses permitted. INCO, patients receiving incobotulinumtoxinA; CON, patients receiving conventional therapy.

Seventy-eight percent of INCO patients and 87% of CON patients had concomitant diseases, mainly vascular disorders (87%). Prior to study entry, antispastic medications were documented for 69% of all patients. All INCO patients were treated by specialists including neurologists and rehabilitation specialists. In CON, 13 % of the patients were treated by specialists. All general practitioners participating in this study chose CON.

Antispastic treatment

In INCO, 38% of the patients were BT naïve. The remainder had received their last BT injection 15.7 weeks (median, range 12-171 weeks) before inclusion in the study. Minimum latency allowed in this study was 12 weeks. IncobotulinumtoxinA doses were 215±114 MU (mouse units; mean ± standard deviation) at V1 and 268.7±155 MU at V5. The most frequently injected muscles were flexor digitorum profundus, flexor digitorum superficialis and biceps brachii. At V1, 35% of INCO patients were receiving oral antispastic medication, mainly baclofen (63%) and tolperisone (21%). At V5, this percentage had dropped to 22%. In CON, 34% of the patients were receiving oral antispastic medication at V1, mainly baclofen (62%), tetrazepam (16%) and tolperisone (11%). At V5, this percentage had dropped to 33%. Non-pharmacological antispasticity treatment is shown in table 4.

Table 4: Number of patients receiving non-pharmacological antispasticity treatment.

	INCO		**CON**	
	First 3 study months (n=108)	Last 3 study months (n=94)	First 3 study months (n=110)	Last 3 study months (n=84)
Physiotherapy	60 (56%)	51 (54%)	68 (62%)	52 (62%)
Occupational therapy	43 (40%)	44 (47%)	15 (14%)	8 (10%)
Speech therapy	10 (9%)	9 (9%)	5 (5%)	4 (5%)
Others	3 (3%)	4 (4%)	3 (3%)	1 (1%)

Data are number of patients (%). Multiple responses permitted. INCO, patients receiving incobotulinumtoxinA; CON, patients receiving conventional therapy.

In INCO, 56% of patients received physiotherapy during the first three study months, 54% during the last. In CON, it was 62% and 62%, respectively. In INCO, 40% of patients received occupational therapy during the first three study months, 47% during the last. In

CON, it was 14% and 10%, respectively. In INCO, 9% of patients received speech therapy during the first three study months, 9% during the last. In CON, it was 5% and 5%, respectively.

Muscle tone

Figure 2 shows the reduction of muscle tone in INCO and CON as measured by the percentage of treatment responders on the AS at V1 and V5/V5b. For all nine clinical patterns of arm spasticity AS responder rates were significantly higher in INCO than in the CON group ($p<0.01$). Logistic regression analyses indicated no relevant influence of baseline characteristics, treatment arm or AS at baseline on the treatment response.

Functional disability

Table 5 shows the reduction of functional disability in INCO and CON as measured by DAS at V1 and V5/V5b.

Table 5: Improvement of disability as measured by the Disability Assessment Scale from V1 to V5/V5b.

Domain	INCO (n=92)	P value	CON (n=83)	P value
Hygiene	-0.7±1.1	< 0.01	-0.2±0.8	< 0.01
Dressing	-0.8±1.0	< 0.01	0.0±0.6	0.85
Limb position	-1.0±0.9	< 0.01	-0.3±0.7	< 0.01
Pain	-0.8±0.9	< 0.01	-0.1±0.9	0.44

Data are mean changes ± SD. Wilcoxon-Mann-Whitney test for p values. INCO, patients receiving incobotulinumtoxinA; CON, patients receiving conventional therapy.

In INCO, functional disability significantly improved from V1 to V5b in all four domains. For hygiene, DAS improvement was -0.7±1.1 ($p<0.01$), for getting dressed -0.8±1.0 ($p<0.01$), for limb position -1.0±0.9 ($p<0.01$) and for pain -0.8±0.9 ($p<0.01$) (mean changes ± SD from baseline to study end). The median for each single domain was -1.0. In CON, DAS improvement for hygiene was -0.2±0.8 ($p<0.01$), for getting dressed 0.0±0.6 ($p=0.85$), for limb position -0.3±0.7 ($p<0.01$) and for pain -0.1±0.9 ($p=0.44$). Median improvements for all four domains in CON were 0.0.

Therapy outcome

In INCO, the most commonly chosen top priority treatment goals at V1 were alleviation of pain (35%) and improvement of finger dexterity (17%); at V5, 29% and 11% of patients, respectively, had chosen these goals. Overall, 93% of INCO patients achieved their top priority treatment goal. Alleviation of pain was attained in all INCO patients, improvement of finger dexterity in 67%. In CON, top priority treatment goals at V1 were improvement of finger dexterity (32%) and alleviation of pain (26%). At final visit, 11% attained improvement of finger dexterity, 48% attained alleviation of pain. Overall, treatment goals with top priority in this group were achieved in 30%.

Global outcome

In INCO, 93% of the physicians and 90% of the patients rated the therapeutic efficacy as 'good' or 'very good', in CON 36% and 37%, respectively (Figure 3). In INCO, 92% of the physicians and 92% of the patients rated tolerability as 'very good', 7% of the physicians and 7% of the patients as 'good'. In CON, 13% of the physicians and 18% of the patients rated tolerability as 'very good', 63% of the physicians and 49% of the patients as 'good'.

Quality of life

In INCO, the physical score increased from 33.6±7.8 (V1) to 42.0±8.4 (V5b) ($p<0.01$), the mental score from 42.8±14.8 (V1) to 52.9±11.0 (V5b) ($p<0.01$) (mean values ± SD). In CON, the mental score increased from 37.8±14.4 (V1) to 41.4±12.5 (V5) ($p=0.02$), the physical score from 35.5±9.3 (V1) to 36.3±8.1 (V5) ($p=0.43$).

Safety

Safety analysis was based on data of 218 patients. Forty-nine patients (22%) experienced 81 AEs. In INCO, 20 AEs in 8% of patients and 21 SAEs in 16% of patients occurred, in CON 18 AEs (in 10% of patients) and 22 SAEs (in 15% of patients). There were no significant differences between the groups ($p=0.439$ for AEs, $p=0.452$ for SAEs). Of the 38 AEs, 79% were mild to moderate, 13% severe. Of the 43 SAEs, 19% were mild to moderate, 67% severe (INCO 48%, CON 87%). All AEs and SAEs but one AE were considered not related to treatment. A 72-year old male INCO patient reported a mild loss of strength in his left arm. Six patients died during the study period, all in CON. None of the deaths were treatment related. 25 patients (15 INCO, 10 CON) prematurely discontinued treatment. Physicians decided to withdraw INCO in three cases (sufficient improvement of condition for two patients, lack of effectiveness for one patient). There was no treatment discontinuation owing to tolerability problems in INCO.

DISCUSSION

This study presents the data of a long-term, multicentre study on the efficacy and safety of incobotulinumtoxinA versus conventional antispastic treatment alone in patients with

poststroke arm spasticity. With 218 patients included in 47 centres in Germany, this is the largest study of its kind.

Spasticity patterns included nine different patterns of arm spasticity among others elbow flexion, wrist flexion, shoulder adduction/internal rotation, finger flexion and forearm pronation. CON treatment included mainly baclofen, tetrazepam and tolperisone accompanied by physiotherapy, occupational therapy and speech therapy. INCO treatment consisted of 215±114 MU at the beginning and 268.7±155 MU at the end of the study accompanied by mainly baclofen, tolperisone, physiotherapy, occupational therapy and speech therapy. BT dose increase is more likely reflecting dose optimization to improve efficacy rather than compensation for BT antibody induced efficacy loss.[14] Thirty-eight percent of patients were BT naïve at study entry. Additional consumption of antispastic drugs was reduced in INCO, reflecting BT efficacy.

Muscle tone measured by responder rates in AS was the primary study parameter. It improved for all spasticity patterns much more in INCO than in CON with responder rates between 63% and 86% (INCO) and 16% and 27% (CON). Functional disability was measured by DAS. In all four domains median improvement was 1.0 in INCO which is considered a clinically meaningful change. [10, 15] In CON, it was 0.0, i.e. nil.

Therapy outcome was measured by GAS. In INCO at study end, 93% of the patients attained their top priority treatment goal, in CON 30%. Relief from muscle pain is a common treatment goal for patients in both early and late stages of upper limb spasticity;[16] a significant decrease in pain ratings was previously shown under long-term BT treatment.[17, 18] Alleviation of pain was the most frequent top priority treatment goal in INCO and the second most frequent in CON. All INCO patients, but only 48% of CON patients reached that goal. Our results demonstrate a significant reduction in pain intensity as well as in functional impairment due to spasticity-related pain in the course of incobotulinumtoxinA treatment.

Global outcome was measured by GCI. Efficacy was rated good and very good in 93% (physicians) and 91% (patients) in INCO. In CON it was 36% and 37%, respectively. Tolerability was rated good and very good in 99% (physicians) and 99% (patients) in INCO. In CON figures were 76% (physicians) and 66% (patients), respectively.

Quality of life as measured by SF-12 improved by 8.0±8.6 (physical score) and 10.8±16.2 (mental score) in INCO, in CON by 5.7±13 (mental score) (mean changes ± SD from baseline to study end). The physical score in CON did not improve (0.8±7.9). Spasticity has a negative impact on the quality of life of stroke survivors, in particular on the physical domain. According to a study published in 2012, US stroke survivors with spasticity had significantly lower SF-12 Health Survey physical domain scores at three months and one year following stroke than stroke patients without spasticity.[19] Increasing functional disability in the DAS domains hygiene, dressing, and pain in upper limb spasticity was significantly associated with diminishing quality of life scores measured by the EuroQol 5 questionnaire.[20] At the start of our study, patients had physical and mental domain scores of 34.5 and 40.5, respectively, which were markedly lower than the scores for the German population norm with 49.6 and 52.3. Safety analysis did not reveal new safety signals or significant differences with respect to treatment received.

Our results confirm results from a randomised placebo-controlled incobotulinumtoxinA trial [21] and a previous long-term open-label study.[22] They are in line with long-term investigations of other BT drugs in the treatment of spasticity of various etiologies including stroke.[17, 23, 24] Underlying paresis in spasticity should be addressed by additional physiotherapy.[4, 25] Successful treatment of spasticity requires an individualised treatment approach and should be managed by a multidisciplinary team.[2, 4]

In summary, treatment of upper limb spasticity over a 1-year treatment period in routine clinical practice was more effective in the incobotulinumtoxinA arm than in the conventional

therapy arm in the assessments performed in this study. Effective poststroke spasticity treatment requires specialised, individualised, and multidisciplinary treatment approaches.

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Contributors

DD: study conception, data interpretation, critical manuscript revision, approval of final manuscript version

RR: study conception, data acquisition, data analysis, data interpretation, critical manuscript revision, approval of final manuscript version

FK: data acquisition, data analysis, data interpretation, critical manuscript revision, approval of final manuscript version

NS: study conception, data analysis, data interpretation, critical manuscript revision, approval of final manuscript version

JLB: study conception, data analysis, data interpretation, critical manuscript revision, approval of final manuscript version

Competing interest

DD received compensation for consultations by Allergan, Bayer, Abbvie, IAB-Arbeitskreis Bewegungsstörungen, Merz Pharmaceuticals, Ipsen, and Syntaxin. NS and JLB are employees of Merz Pharmaceuticals GmbH, Frankfurt/M, Germany. RR and FK are employees of Institute of Empirical Health Economics, Burscheid, Germany.

Ethics approval

Ethics committee of Hannover Medical School, Germany.

Data sharing

No additional data available.

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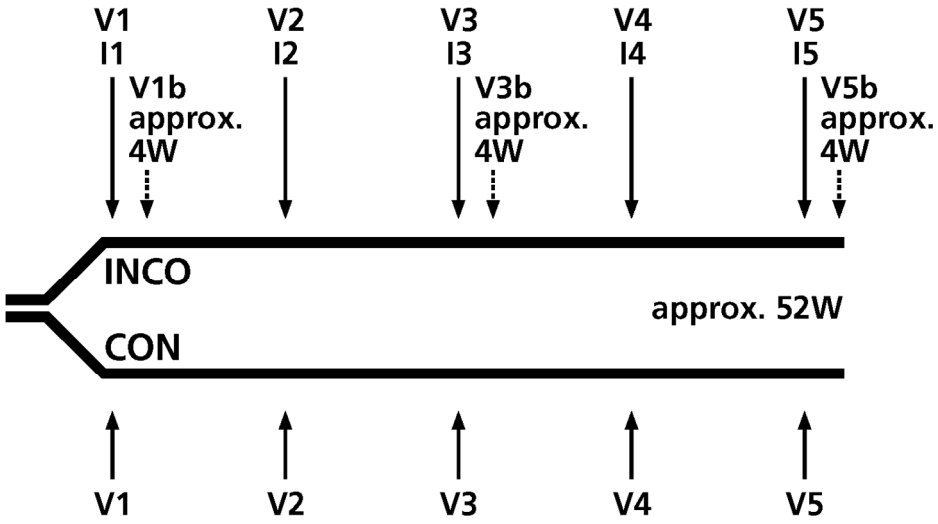
FIGURES

Figure 1: Study design. CON, patients receiving conventional therapy; I, injection; INCO, patients receiving incobotulinumtoxinA; V, visit; W, weeks.

Figure 2: Improvement of muscle tone from V1 to V5/V5b in the incobotulinumtoxinA group (INCO) and in patients receiving conventional therapy (CON) for all spasticity patterns as shown by the percentage of treatment responders. Treatment response was defined as an Ashworth Score improvement of ≥1. * $p<0.01$ (Fisher's exact test).

Figure 3: Improvement of global clinical impression from V1 to V5/V5b. **A.** Physician assessment (n=85 in INCO, n=75 in CON). **B.** Patient assessment (n=84 in INCO, n=74 in CON). INCO, patients receiving incobotulinumtoxinA; CON, patients receiving conventional therapy.



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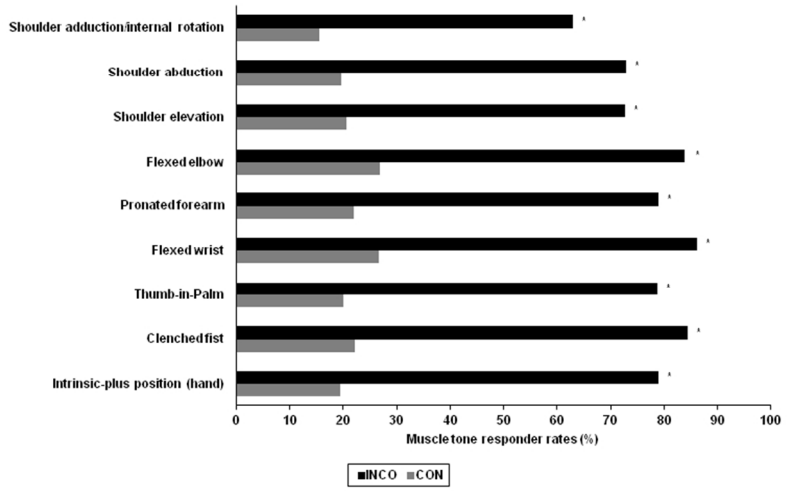

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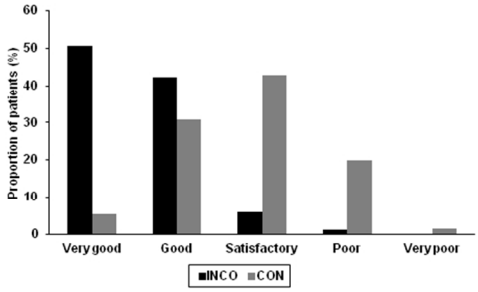

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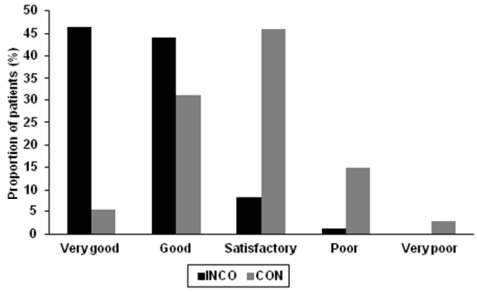

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **In abstract**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ✓
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **page 4**
Objectives	3	State specific objectives, including any prespecified hypotheses **page 4**
Methods		
Study design	4	Present key elements of study design early in the paper **page 4/5, Figure 1**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **pages 5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **page 5** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **pages 6/7**
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 **pages 6/7**
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
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 **page 7/8**
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed **page 8**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 2, page 9**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **pages 11-14, Tables 3-5, Figures 2/3**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
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
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives ✓
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 **page 3**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ✓
Generalisability	21	Discuss the generalisability (external validity) of the study results ✓
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 ✓

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.

BMJ Open

Long-Term Efficacy and Safety of IncobotulinumtoxinA and Conventional Treatment of Poststroke Arm Spasticity – a Prospective, Non-Interventional, Open-Label, Parallel-Group Study

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Primary Subject Heading:	Neurology
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Keywords:	muscle spasticity, botulinum toxins, type A, outcome assessments

Long-Term Efficacy and Safety of IncobotulinumtoxinA and Conventional Treatment of Poststroke Arm Spasticity – a Prospective, Non-Interventional, Open-Label, Parallel-Group Study

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Keywords: muscle spasticity, botulinum toxins, type A, outcome assessments

Word count (text only): 2827 words

ABSTRACT

Objective: To compare efficacy and safety of incobotulinumtoxinA to conventional antispastic therapy for poststroke arm spasticity in routine clinical practice over a 1-year period.

Design: Prospective, non-interventional, open-label, parallel-group study.

Setting: Forty-seven centres in Germany.

Participants: Patients with poststroke arm spasticity; 108 receiving incobotulinumtoxinA, 110 conventional therapy.

Intervention: Conventional antispastic treatment including oral antispastic medications, physiotherapy and occupational therapy or 3-monthly incobotulinumtoxinA injections plus conventional therapy if required.

Main outcome measures: The main outcome measure was changes in muscle tone (Ashworth Scale) over the 1-year treatment period. Changes in functional disability (Disability Assessment Scale) and quality of life (Short-Form-12 Health Survey) were additionally assessed. Ratings for therapy outcome (Goal Attainment Scale), and efficacy and tolerability of treatment (Global Clinical Impression Scale) were also obtained.

Results: Muscle tone improved for all spasticity patterns with Ashworth Scale responder rates between 63%- 86% (incobotulinumtoxinA) and 16%-27% (conventional therapy). Median improvement in functional disability was -1.0 (incobotulinumtoxinA) and 0.0 (conventional measures) for all domains. Treatment goals were attained by 93% of incobotulinumtoxinA patients and 30% of patients under conventional therapy. Most physicians (93%) and patients (90%) rated efficacy as good or very good under incobotulinumtoxinA; the proportions were much lower under conventional therapy (36% and 37%). Tolerability under incobotulinumtoxinA was considered good or very good by 99% of physicians and patients (76% and 66% respectively, under conventional therapy). Quality of life under

incobotulinumtoxinA improved by 8.0 (physical score) and 10.8 (mental score) and by 0.8 and 5.7, respectively, under conventional therapy.

Conclusions: IncobotulinumtoxinA combined with rehabilitation and oral medication produces a much more robust improvement in all aspects of arm spasticity than conventional antispastic treatment. Effects are stable over a period of 1 year, adverse effects are negligible. IncobotulinumtoxinA should be considered treatment of choice for poststroke arm spasticity.

Strengths and limitations of this study

- This is the largest study of its kind carried out in Germany.
- There is a potential bias because of the 100% participation of specialist physicians in the incobotulinumtoxinA arm compared to only 11% in the conventional therapy arm: their greater expertise in the treatment of spasticity compared to general practitioners provided more patients with additional antispastic measures which might have increased the benefits of botulinum toxin treatment.
- The non-interventional study design reflects the real-world health care situation in Germany in the treatment of poststroke spasticity.

INTRODUCTION

Spasticity is a common complication of motor stroke. It is often more pronounced in arm than in leg muscles and occurs in approximately 30% of patients suffering from motor stroke.[1] Patients with poststroke spasticity often experience marked functional impairments which may result in restrictions in their daily routine, in dependence on assistance from family and/or caregivers and in impaired social participation.[2] This may lead to loss of self-esteem, poor body image, depression and a diminished quality of life. Conventional treatment options are numerous, efficacy, however, is limited. For adult upper limb spasticity, the use of botulinum toxin (BT) therapy is supported by various guidelines, expert opinions and a recent evidence-based review.[2-6] However, an analysis of claims data from a large statutory German health insurance fund found that none in the cohort received BT treatment for poststroke spasticity. [7] BT therapy for spasticity thus seems to have so far not been implemented in routine health care practice in Germany and cannot as yet be considered a conventional treatment approach.

Our study assessed the effectiveness and safety of different therapeutic measures for arm spasticity after stroke in routine clinical practice in Germany over a 1-year period and compared the administration of conventional measures including oral antispastic medications, physiotherapy and occupational therapy to BT therapy. The primary assessment parameter was the change in muscle tone over the treatment period. Additionally, changes in functional disability and quality of life were assessed, and physicians and patients rated goal attainment and treatment efficacy and safety.

METHODS

Study Design

This study was based on a prospective, non-interventional, open-label, multicentre, parallel-group design. In CON, patients received conventional antispastic treatment including oral

antispastic medications, physiotherapy and occupational therapy at the physician's discretion. In INCO, patients received incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, Frankfurt/M, Germany [8]) and additionally conventional treatment, if required. General practitioners and specialists including neurologists and rehabilitation specialists were invited to participate in this study. Prior to initiation of the study, they had to choose which spasticity treatment they wanted to administer and were thus included in the CON or INCO treatment arm. All treatment decisions were made before inclusion of the patient in the study. IncobotulinumtoxinA was applied according to the physician's decision with respect to dose and muscles injected. Any kind of antispastic treatment, procedures as well as medications, were documented. Participating physicians were asked to document the first four eligible patients presenting at their practice using standardised report forms. Up to 16 patients could be included per site.

The patient flow in this study is shown in figure 1. At baseline visit (V1), all patients were prescribed their respective antispastic treatment and INCO patients received their first incobotulinumtoxinA injections. Patients then presented every three months for follow-ups at visits V2 (month 3), V3 (month 6), V4 (month 9) and V5 (month 12) when INCO patients received their subsequent incobotulinumtoxinA injections. To document maximum incobotulinumtoxinA efficacy, INCO patients were additionally evaluated 4 weeks after V1, V3 and V5, respectively, at V1b, V3b and V5b.

The study was approved by the ethics committee of Hannover Medical School and conducted by the Institute of Empirical Health Economics, Burscheid, Germany at 47 centres in Germany between April 2012 and May 2014 in accordance with section 4, subsection 23 and section 67, subsection 6 of the Medicinal Products Act of the Federal Republic of Germany. All participating patients gave written informed consent.

Patients

Inclusion criteria included diagnosis of poststroke arm spasticity, indication for antispastic treatment, adult age (at least 18 years old), ability to read and to understand the study information material and to complete the patient questionnaire. Exclusion criteria included simultaneous participation in another spasticity trial, application of BT less than 12 weeks before inclusion in this study, hypersensitivity to BT drugs or their individual contents, infection at the intended injection site and presence of neuromuscular disorders such as myasthenia gravis and Lambert-Eaton syndrome.

Parameters

As primary assessment parameter, changes in muscle tone was evaluated with a responder analysis for all clinical patterns of upper limb spasticity. Muscle tone was evaluated with the *Ashworth Scale* (AS; Grade 0: no increase in muscle tone; Grade 1: slight increase in muscle tone, giving a catch when the affected limb is moved in flexion or extension; Grade 2: more marked increase in muscle tone, but limb easily flexed; Grade 3: considerable increase in muscle tone, passive movement difficult; Grade 4: limb rigid in flexion or extension).[9] A reduction by at least one point was considered clinically meaningful. Patients with a clinically meaningful response were considered responders.

Functional disability was rated by the *Disability Assessment Scale* (DAS) for the four domains hygiene, getting dressed, limb position and pain (Grade 0: no disability; Grade 1: mild disability; Grade 2: moderate disability; Grade 3: severe disability).[10] A reduction by at least one point was considered clinically meaningful.

Therapy outcome was documented by a simplified version of the *Goal Attainment Scale* (GAS).[11] During each visit, patients and physicians chose three treatment goals (priority rating 1, 2, and 3) they wanted to attain over the next three months from a list of 17 items. For documentation, physicians only documented if the treatment goal was attained or not. The list of goals is shown in table 1.

Table 1: List of treatment goals. At each visit patients chose three treatment goals they wanted to attain until the next visit.

Pain relief
Reduction of frequency of muscle spasms
Reduction of involuntary movements
Improvement of dexterity
Improvement of self care: personal hygiene
Improvement of self-care: eating
Improvement of sexual activity
Prevention of contractures and deformation
Improvement of self care: hand hygiene
Improved body image
Improved fit of clothing
Facilitation of rehabilitation
Reduction of use of systemic medication in antispasticity treatment
Reduction of daily care measures
Reduction of care measures regarding movements
Easier application of (arm) splints and extended usage
Reduction/prevention of surgical interventions

Global Clinical Impression (GCI) of effectiveness and tolerability of the respective treatment was rated by patients and physicians separately at the end of the observation period as very good, good, satisfactory, poor, or very poor.

Quality of life was rated by the patients with the *SF-12v2 Health Survey,* a shorter version of the SF-36 Health Survey.[12] The 12 SF-12 Health Survey items are subsumed under the

dimensions 'mental health' and 'physical health'. Possible scores in both domains range from 0 to 100, higher scores indicating a higher quality of life.

To assess safety, physicians monitored the occurrence of *adverse events* (AE) and *serious adverse events* (SAE) during the entire 1-year observation period.

Statistical Analysis

Documented data were processed with single data entry using Oracle Database Online Documentation 11g Release 2 (Oracle, Redwood Shores, CA, USA). All data were checked for completeness, consistency and plausibility. The efficacy analysis included all patients in INCO or CON for at least three months. Except for the primary parameter, all analyses were descriptive and exploratory. Missing data were not imputed. End of observation time point was V5 for CON and V5b for INCO. The primary study parameter (changes in AS) was evaluated with a responder analysis for all clinical patterns of upper limb spasticity. All patients with baseline AS ≥1 were included in the respective analysis. Treatment response was defined as AS improvement ≥1 from baseline to end of the observation period. Fisher's exact test was used for comparison of treatment response between INCO and CON. The influence on treatment response regarding the independent variables gender, height, weight, body mass index, age, time since stroke, duration of spasticity, treatment arm and baseline AS (for the investigated clinical patterns) was tested using logistic regression analyses. P values for DAS changes over the course of the study were calculated with the Wilcoxon-Mann-Whitney test. SF-12 Health Survey changes were evaluated using the physical and the mental component score. Scores were calculated using a fixed algorithm and were based on the analysis manual of the German norm from 1994.[13] Comparisons of SF-12 Health Survey scores between baseline and end of observation employed the paired t-test. All patients receiving antispastic treatment at least once during the observation period were included in the tolerability analysis. AEs were encoded with the Medical Dictionary for Regulatory

Activities version 13.0 (MedDRA). The Chi-square test was used to compare AE incidences between the treatment arms.

RESULTS

Demographics

Table 2 summarises the baseline characteristics of the two study groups; 108 patients were included in the INCO group at 21 study sites, 110 patients in the CON group at 26 study sites.

Table 2: Demographic and baseline characteristics of the study population at V1.

	INCO (n=108)	**CON (n=110)**
Male gender [n]	58 (53.7%)	70 (63.6%)
Female gender [n]	50 (46.3%)	40 (36.4%)
Age [years]	61.7±12.9	67.8±12.7
Body mass index [kg/m^2]	26.7±4.1	27.7±4.8
Time since stroke [years]	7.5±5.8	5.3±5.1
Type of stroke		
ischemic	51 (47.2%)	43 (39.1%)
haemorrhagic	16 (14.8%)	7 (6.4%)
others	21 (19.4%)	29 (26.4%)
no data	20 (18.5%)	31 (28.2%)
Duration of upper limb spasticity [years]	6.6±6.3	4.9±5.4
Previous antispastic medication [n]	85 (78.7%)	65 (59.1%)
Previous botulinum toxin therapy [n]	67 (62%)	0

Data are mean ± standard deviation or number of patients (%). INCO, patients receiving incobotulinumtoxinA; CON, patients receiving conventional therapy.

Eighty-nine percent of the patients completed the observation period. Fifty-seven percent of all patients presented with combined arm and leg spasticity; 54% (INCO) and 32% (CON) had arm spasticity only. The most frequent clinical spasticity patterns were flexed elbow (86%), flexed wrist (72%), shoulder adduction/internal rotation (71%), clenched fist (71%) and forearm pronation (71%). As shown in table 2, INCO patients had suffered from spasticity for a longer period of time with a higher proportion of patients with AS ≥2 in most of the clinical patterns at baseline than CON patients (table 3).

Table 3: Clinical patterns of arm spasticity in patients with a baseline severity in Ashworth score ≥2 at V1.

	INCO (n=108)	**CON (n=110)**
Flexed elbow	91 (84.3%)	59 (53.6%)
Clenched fist	77 (71.3%)	40 (36.4%)
Flexed wrist	67 (62.1%)	58 (52.7%)
Pronated forearm	63 (58.3%)	49 (44.6%)
Thumb-in-palm	53 (49.1%)	43 (39.1%)
Shoulder adduction and internal arm rotation	52 (48.2%)	40 (36.3%)
Shoulder abduction	36 (33.3%)	45 (40.9%)
Shoulder elevation	32 (29.6%)	46 (41.8%)
Intrinsic plus hand	20 (18.5%)	33 (30.0%)

Data are number of patients (%). Multiple responses permitted. INCO, patients receiving incobotulinumtoxinA; CON, patients receiving conventional therapy.

Seventy-eight percent of INCO patients and 87% of CON patients had concomitant diseases, mainly vascular disorders (87%). Prior to study entry, antispastic medications were documented for 69% of all patients. All INCO patients were treated by specialists including neurologists and rehabilitation specialists. In CON, 13% of the patients were treated by specialists. All general practitioners participating in this study chose conventional antispastic treatment.

Antispastic treatment

In the INCO group, 38% of the patients were BT naïve. The remainder had received their last BT injection 15.7 weeks (median, range 12-171 weeks) before inclusion in the study. Minimum latency allowed in this study was 12 weeks. IncobotulinumtoxinA doses were 215±114 MU (mouse units; mean ± standard deviation) at V1 and 268.7±155 MU at V5. The most frequently injected muscles were flexor digitorum profundus, flexor digitorum superficialis and biceps brachii. At V1, 35% of INCO patients were receiving oral antispastic medication, mainly baclofen (63%) and tolperisone (21%). At V5, this percentage had dropped to 22%. In the CON group, 34% of the patients were receiving oral antispastic medication at V1, mainly baclofen (62%), tetrazepam (16%) and tolperisone (11%). At V5, this percentage had dropped to 33%. Non-pharmacological antispasticity treatment is shown in table 4.

Table 4: Number of patients receiving non-pharmacological antispasticity treatment.

	INCO		**CON**	
	First 3 study months	Last 3 study months	First 3 study months	Last 3 study months

	(n=108)	(n=94)	(n=110)	(n=84)
Physiotherapy	60 (56%)	51 (54%)	68 (62%)	52 (62%)
Occupational therapy	43 (40%)	44 (47%)	15 (14%)	8 (10%)
Speech therapy	10 (9%)	9 (9%)	5 (5%)	4 (5%)
Others	3 (3%)	4 (4%)	3 (3%)	1 (1%)

Data are number of patients (%). Multiple responses permitted. INCO, patients receiving incobotulinumtoxinA; CON, patients receiving conventional therapy.

In the INCO group, 56% of patients received physiotherapy during the first three study months, 54% during the last. Under conventional therapy, these were 62% and 62% of the patients, respectively. Occupational therapy was prescribed for 40% of INCO patients during the first three study months and 47% during the last compared to 14% and 10%, respectively, under conventional antispastic therapy. In the INCO group, 9% of patients received speech therapy during the first three study months, 9% during the last (5% of CON patients for both periods). Intensity of the different therapies was not documented.

Muscle tone

Figure 2 shows the reduction of muscle tone in INCO and CON as measured by the percentage of treatment responders on the AS at V1 and V5/V5b. For all nine clinical patterns of arm spasticity AS responder rates were significantly higher in the INCO than in the CON group ($p<0.01$). Logistic regression analyses indicated no relevant influence of baseline characteristics, treatment arm or AS at baseline on the treatment response.

Functional disability

Table 5 shows the reduction of functional disability in INCO and CON as measured by DAS at V1 and V5/V5b.

Table 5: Improvement of disability as measured by the Disability Assessment Scale from V1 to V5/V5b.

Domain	INCO (n=92)	P value	CON (n=83)	P value
Hygiene	-0.7±1.1	< 0.01	-0.2±0.8	< 0.01
Dressing	-0.8±1.0	< 0.01	0.0±0.6	0.85
Limb position	-1.0±0.9	< 0.01	-0.3±0.7	< 0.01
Pain	-0.8±0.9	< 0.01	-0.1±0.9	0.44

Data are mean changes ± SD. Wilcoxon-Mann-Whitney test for p values. INCO, patients receiving incobotulinumtoxinA; CON, patients receiving conventional therapy.

In the INCO group, functional disability significantly improved from V1 to V5b in all four domains. For hygiene, DAS improvement was -0.7±1.1 ($p<0.01$), for getting dressed -0.8±1.0 ($p<0.01$), for limb position -1.0±0.9 ($p<0.01$) and for pain -0.8±0.9 ($p<0.01$) (mean changes ± SD from baseline to study end). The median for each single domain was -1.0. In the CON group, DAS improvement for hygiene was -0.2±0.8 ($p<0.01$), for getting dressed 0.0±0.6 ($p=0.85$), for limb position -0.3±0.7 ($p<0.01$) and for pain -0.1±0.9 ($p=0.44$). Median improvements for all four domains in CON were 0.0.

Therapy outcome

In the INCO group, the most commonly chosen top priority treatment goals at V1 were alleviation of pain (35%) and improvement of finger dexterity (17%); at V5, 29% and 11% of patients, respectively, had chosen these goals. Overall, 93% of INCO patients achieved their top priority treatment goal. Alleviation of pain was attained in all INCO patients,

improvement of finger dexterity in 67%. In the CON group, top priority treatment goals at V1 were improvement of finger dexterity (32%) and alleviation of pain (26%). At final visit, 11% attained improvement of finger dexterity, 48% attained alleviation of pain. Overall, treatment goals with top priority in this group were achieved in 30%.

Global outcome

In the INCO group, 93% of the physicians and 90% of the patients rated the therapeutic efficacy as 'good' or 'very good', in the CON group 36% and 37%, respectively (Figure 3A and Figure 3B). Tolerability of INCO treatment was rated as ‘very good’ by 92% of both physicians and patients; 7% of both physicians and patients considered it as 'good'. In the CON group, 13% of the physicians and 18% of the patients rated tolerability as 'very good', 63% of the physicians and 49% of the patients as 'good'.

Quality of life

In the INCO group, the physical score increased from 33.6±7.8 (V1) to 42.0±8.4 (V5b) ($p<0.01$), the mental score from 42.8±14.8 (V1) to 52.9±11.0 (V5b) ($p<0.01$) (mean values ± SD). In the CON group, the mental score increased from 37.8±14.4 (V1) to 41.4±12.5 (V5) ($p=0.02$), the physical score from 35.5±9.3 (V1) to 36.3±8.1 (V5) ($p=0.43$).

Safety

Safety analysis was based on data of 218 patients. Forty-nine patients (22%) experienced 81 AEs. Twenty AEs occurred in 8% and 21 SAEs in 16% of INCO patients;18 AEs (in 10% of patients) and 22 SAEs (in 15% of patients) were observed in the CON group. There were no significant differences between the groups ($p=0.439$ for AEs, $p=0.452$ for SAEs). Of the 38 AEs, 79% were mild to moderate, 13% severe. Of the 43 SAEs, 19% were mild to moderate,

67% severe (INCO 48%, CON 87%). All AEs and SAEs but one AE were considered not related to treatment. A 72-year old male INCO patient reported a mild loss of strength in his left arm. Six patients died during the study period, all in the CON group. None of the deaths were treatment related. 25 patients (15 INCO, 10 CON) prematurely discontinued treatment. Physicians decided to withdraw incobotulinumtoxinA treatment in three cases (sufficient improvement of condition for two patients, lack of effectiveness for one patient). There was no treatment discontinuation owing to tolerability problems in the INCO group.

DISCUSSION

This study presents the data of a long-term, multicentre study on the efficacy and safety of incobotulinumtoxinA versus conventional antispastic treatment alone in patients with poststroke arm spasticity. With 218 patients included in 47 centres in Germany, this is the largest study of its kind.

Spasticity patterns included nine different patterns of arm spasticity among others elbow flexion, wrist flexion, shoulder adduction/internal rotation, finger flexion and forearm pronation. Conventional antispastic treatment included mainly baclofen, tetrazepam and tolperisone accompanied by physiotherapy, occupational therapy and speech therapy. BT treatment consisted of 215±114 MU incobotulinumtoxinA at the beginning and 268.7±155 MU at the end of the study accompanied by mainly baclofen, tolperisone, physiotherapy, occupational therapy and speech therapy. BT dose increase is more likely reflecting dose optimization to improve efficacy rather than compensation for BT antibody induced efficacy loss.[14] Thirty-eight percent of patients were BT naïve at study entry. Additional consumption of antispastic drugs was reduced in the incobotulinumtoxinA group, reflecting BT efficacy.

Regular incobotulinumtoxinA injections over a one-year period resulted in sustained improvements in muscle tone and functional disability. Between 63% and 86% of the patients

depending on the investigated clinical pattern were treatment responders as measured with the Ashworth scale, and functional disability significantly improved in all four DAS domains. IncobotulinumtoxinA was well tolerated and patients and physicians rated effectiveness and tolerability of the treatment very positively. The treatment was more effective than conventional antispastic therapy; the improvements in muscle tone in particular were more pronounced with a significant difference in responder rates for all nine clinical patterns. Under incobotulinumtoxinA, functional disability improved in all four domains with a median of 1.0 which is considered a clinically meaningful change. [10, 15] Improvements under conventional treatment were 0.0, i.e. nil.

At study end, 93% of the patients receiving incobotulinumtoxinA attained their top priority treatment goal; this was only achieved in 30% of patients under conventional therapy. Relief from muscle pain is a common treatment goal for patients in both early and late stages of upper limb spasticity;[16] a significant decrease in pain ratings was previously shown under long-term BT treatment.[17, 18] Alleviation of pain was the most frequent top priority treatment goal under incobotulinumtoxinA and the second most frequent under conventional therapy. All incobotulinumtoxinA patients but only 48% of patients under conventional antispastic treatment reached that goal. Our results demonstrate a significant reduction in pain intensity as well as in functional impairment due to spasticity-related pain in the course of incobotulinumtoxinA treatment.

Mental quality of life scores improved under both treatments but improvement in the physical component score was only observed in incobotulinumtoxinA patients. Spasticity has a negative impact on the quality of life of stroke survivors, in particular on the physical domain. According to a study published in 2012, US stroke survivors with spasticity had significantly lower SF-12 Health Survey physical domain scores at three months and one year following stroke than stroke patients without spasticity.[19] Increasing functional disability in the DAS domains hygiene, dressing, and pain in upper limb spasticity was significantly associated with

diminishing quality of life scores measured by the EuroQol 5 questionnaire.[20] At the start of our study, patients had physical and mental domain scores of 34.5 and 40.5, respectively, which were markedly lower than the scores for the German population norm with 49.6 and 52.3.

Our results confirm results from a randomised placebo-controlled incobotulinumtoxinA trial [21] and a previous long-term open-label study.[22] They are in line with long-term investigations of other BT drugs in the treatment of spasticity of various etiologies including stroke.[17, 23, 24] Underlying paresis in spasticity should be addressed by additional physiotherapy.[4, 25] Successful treatment of spasticity requires an individualised treatment approach and should be managed by a multidisciplinary team.[2, 4]

A non-interventional study design evaluates the administration of medications under routine clinical practice conditions ('real life' data) and complements randomized controlled trials with a predefined protocol and strict inclusion/exclusion criteria. Treatment decisions are solely at the discretion of the participating physicians and the decision how to treat a particular patient (in this study with conventional therapy or with incobotulinumtoxinA) must be made before inclusion of the patient in the study. The markedly greater improvements in muscle tone and functional ability under incobotulinumtoxinA compared to conventional therapy in this study thus reflect outcomes of day-to-day treatment decisions in general and specialist practices. It should, however, be noted that the 100% participation of specialist physicians in the incobotulinumtoxinA arm compared to only 11% in the conventional therapy arm might have introduced a bias. Physicians in Germany do not require an official certificate to offer botulinumtoxin treatment, however, special training is necessary to gain sufficient expertise. The greater expertise of the specialists in the treatment of spasticity compared to general practitioners provided more patients with additional non-pharmacological antispastic measures which might have increased the benefits of BT

treatment. Intensity of the different procedures applied was not documented and can therefore not be discussed. However, patients in the incobotulinumtoxinA arm received overall better care than patients under conventional therapy. Although the prescription of physiotherapy was similar between the groups, 47% of patients under incobotulinumtoxinA received additional occupational therapy in the last 3 study months compared to only 10% under conventional therapy.

In summary, treatment of upper limb spasticity over a 1-year treatment period in routine clinical practice was more effective in the incobotulinumtoxinA arm than in the conventional therapy arm in the assessments performed in this study. Effective poststroke spasticity treatment requires specialised, individualised, and multidisciplinary treatment approaches. Lack of information about adequate or additional treatment options, the limited number of specialised physicians/BT therapy centres, and inadequate reimbursement of physicians offering BT treatment should be considered by potential stake holders in the German health care system to improve spasticity treatment.

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Contributors

DD: study conception, data interpretation, critical manuscript revision, approval of final manuscript version

RR: study conception, data acquisition, data analysis, data interpretation, critical manuscript revision, approval of final manuscript version

FK: data acquisition, data analysis, data interpretation, critical manuscript revision, approval of final manuscript version

NS: study conception, data analysis, data interpretation, critical manuscript revision, approval of final manuscript version

JLB: study conception, data analysis, data interpretation, critical manuscript revision, approval of final manuscript version

Competing interest

DD received compensation for consultations by Allergan, Bayer, Abbvie, IAB-Arbeitskreis Bewegungsstörungen, Merz Pharmaceuticals, Ipsen, and Syntaxin. NS and JLB are employees of Merz Pharmaceuticals GmbH, Frankfurt/M, Germany. RR and FK are employees of Institute of Empirical Health Economics, Burscheid, Germany.

Ethics approval

Ethics committee of Hannover Medical School, Germany.

Data sharing

No additional data available.

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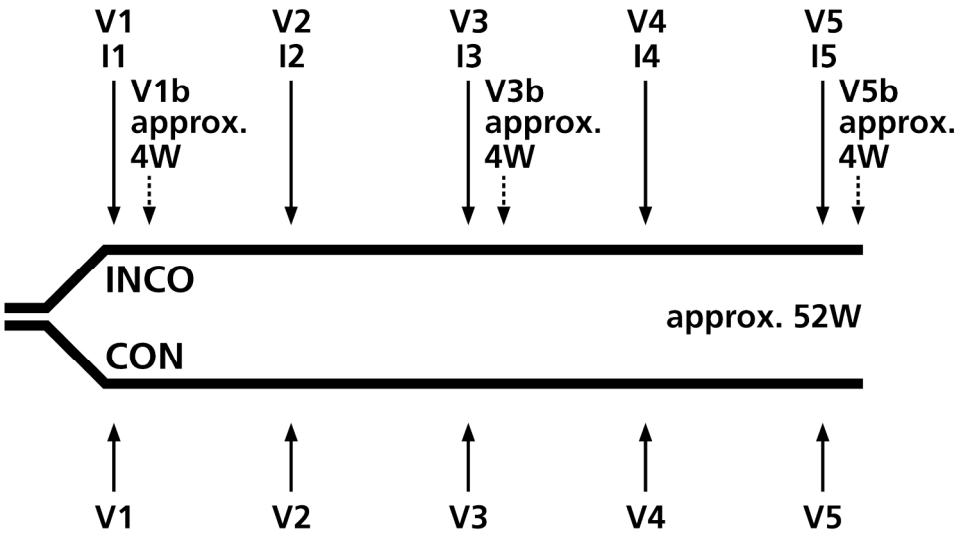
FIGURES

Figure 1: Study design. CON, patients receiving conventional therapy; I, injection; INCO, patients receiving incobotulinumtoxinA; V, visit; W, weeks.

Figure 2: Improvement of muscle tone from V1 to V5/V5b in the incobotulinumtoxinA group (INCO) and in patients receiving conventional therapy (CON) for all spasticity patterns as shown by the percentage of treatment responders. Treatment response was defined as an Ashworth Score improvement of ≥1. * $p<0.01$ (Fisher's exact test).

Figure 3: Improvement of global clinical impression from V1 to V5/V5b. **A.** Physician assessment (n=85 in INCO, n=75 in CON). **B.** Patient assessment (n=84 in INCO, n=74 in CON). INCO, patients receiving incobotulinumtoxinA; CON, patients receiving conventional therapy.



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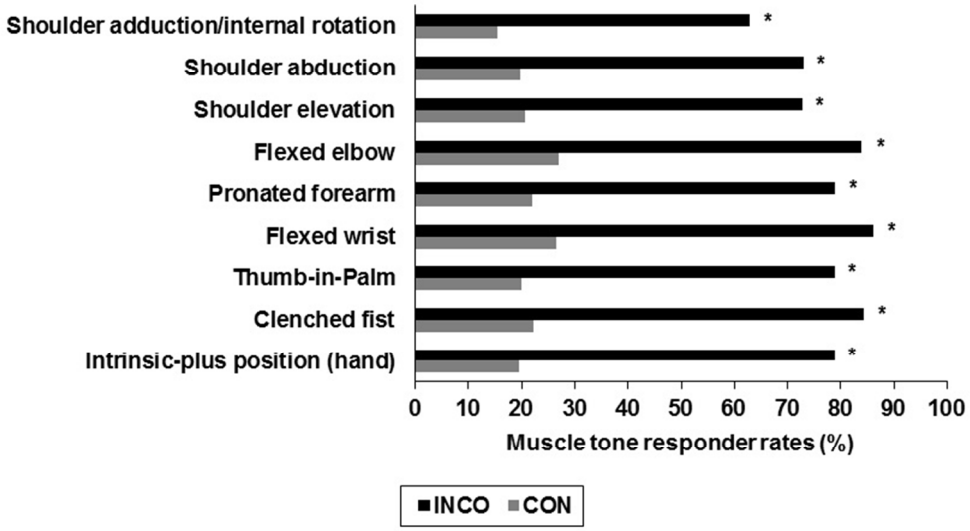

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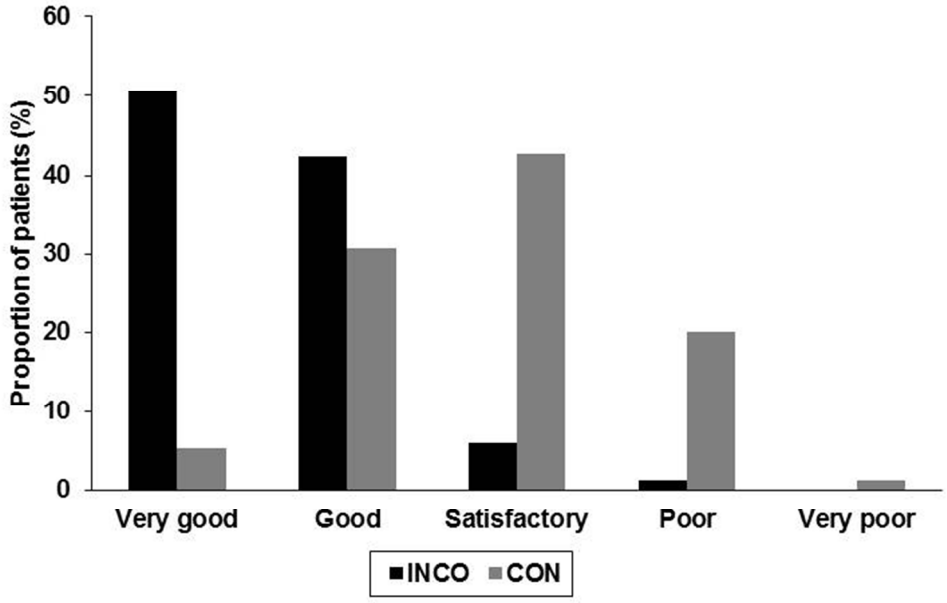

Figure 3: Improvement of global clinical impression from V1 to V5/V5b. A. Physician assessment (n=85 in INCO, n=75 in CON).
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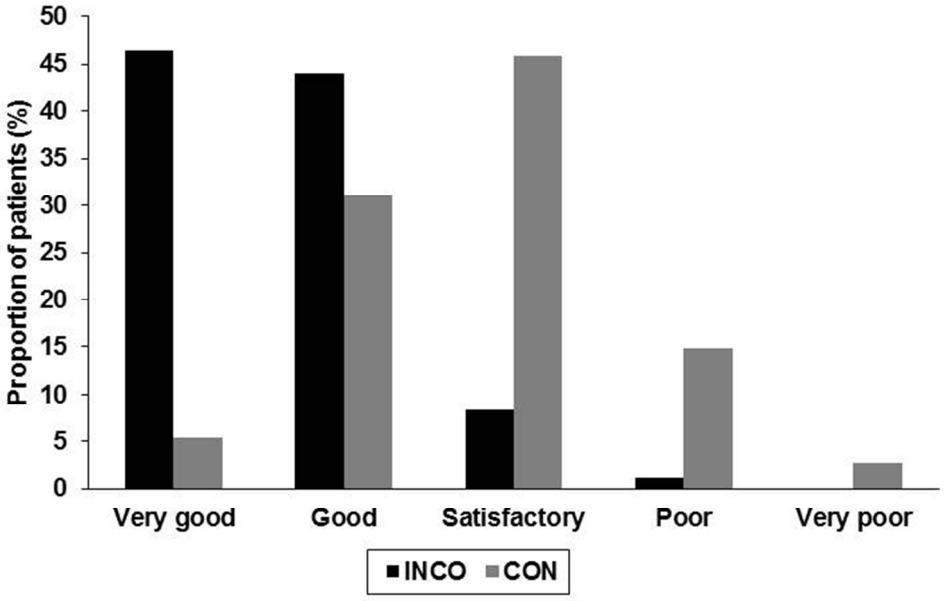

Figure 3: Improvement of global clinical impression from V1 to V5/V5b. B. Patient assessment (n=84 in INCO, n=74 in CON). INCO, patients receiving incobotulinumtoxinA; CON, patients receiving conventional therapy.
63x39mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational 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 **In abstract**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ✓
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **page 4**
Objectives	3	State specific objectives, including any prespecified hypotheses **page 4**
Methods		
Study design	4	Present key elements of study design early in the paper **page 4/5, Figure 1**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **pages 5**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **page 5** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **pages 6/7**
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 **pages 6/7**
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
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 **page 7/8**
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed **page 8**
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

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
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 2, page 9**
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **pages 11-14, Tables 3-5, Figures 2/3**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
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
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives ✓
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 **page 3**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ✓
Generalisability	21	Discuss the generalisability (external validity) of the study results ✓
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 ✓

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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 www.strobe-statement.org.