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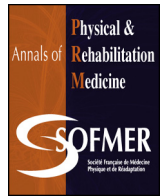


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Original article

Efficacy of incobotulinumtoxinA for the treatment of adult lower-limb post-stroke spasticity, including pes equinovarus



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ABSTRACT

Background: Lower-limb spasticity can impair ambulation and gait, impacting quality of life.

Objectives: This ancillary analysis of the TOWER study (NCT01603459) assessed the efficacy of incobotulinumtoxinA for lower-limb post-stroke spasticity including pes equinovarus.

Methods: Participants received escalating incobotulinumtoxinA doses (400–800 U) across 3 injection cycles. Changes were compared for those treated in the lower limb (with/without upper-limb treatment) or the upper limb only or for participants treated or untreated for pes equinovarus. Outcome measures were those used in the seminal study: resistance to passive movement scale (REPAS), Ashworth Scale (AS), functional ambulation and lower-limb goal attainment.

Results: Among 132/155 (85%) participants with post-stroke spasticity, in cycles 1, 2 and 3, 99, 119 and 121 participants received lower-limb treatment with mean (SD) total limb incobotulinumtoxinA doses of 189.2 (99.2), 257.1 (115.0) and 321.3 (129.2) U, respectively. Of these, 80, 105 and 107, respectively, were treated for pes equinovarus. The mean (SD) improvement in REPAS lower-limb score was greater with treatment in the lower limb versus the upper limb only: -1.6 (2.1) versus -0.4 (1.4); -1.9 (1.9) versus -0.6 (1.6); -2.2 (2.2) versus -1.0 (0.0) ($P = 0.0005$, $P = 0.0133$ and $P = 0.3581$; analysis of covariance [ANCOVA], between-group differences) in cycles 1, 2 and 3, respectively. For all cycles, the mean improvement in ankle joint AS score from injection to 4 weeks post-treatment was greater for participants treated versus not treated for pes equinovarus, with a significant between-group difference in cycle 1 ($P = 0.0099$; ANCOVA). At the end of cycle 3, 42% of participants walked independently and 63% achieved 2 of 2 lower-limb treatment goals (baseline 23% and 34%, respectively).

Conclusions: This study supports the efficacy of incobotulinumtoxinA for treatment of pes equinovarus and other patterns of lower-limb post-stroke spasticity.

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1. Introduction

Post-stroke spasticity is estimated to affect up to 43% of stroke survivors [1,2] and results in a substantial impact on the lives of patients and their carers [3]. Although a higher degree of spasticity (modified Ashworth Scale [MAS] score ≥ 3) is more frequent in the upper- than lower-limb muscles of stroke survivors, the prevalence of lower- and upper-limb spasticity is similar [2]. Furthermore, lower-limb spasticity, including pes equinovarus, can impair ambulation and gait, leading to a

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substantial negative impact on the activities of daily living and health-related quality of life [4,5].

Treatment guidelines recommend that botulinum neurotoxin (BoNT) injections be offered for focal spasticity of the upper and lower limbs [6–10]. Such recommendations are largely based on extensive safety and efficacy data from well-designed clinical trials in adults with upper-limb spasticity [11–18]. There are fewer data reporting the efficacy of BoNT in well-designed clinical trials in adults with lower-limb spasticity [4,19–24]. In addition, given the impact of lower-limb spasticity on ambulation and motor function [5], conclusive data to support the efficacy of BoNT treatment for functional improvement is lacking [25].

The limited clinical evidence supporting lower-limb BoNT treatment may be a consequence of dose limitations in current product licences. Many individuals experience multifocal spasticity of the upper and lower limbs combined [2,26], and in these people, the BoNT dose required to effectively treat all clinical patterns (postural presentations) is likely to exceed the currently recommended maximum total body doses. Thus, physicians may have to prioritise clinical patterns for treatment that will have the greatest impact on individuals' treatment goals and needs [27], and lower-limb treatment may be deprioritised.

Higher than currently recommended incobotulinumtoxinA doses have been generally well tolerated, with no indication of systemic toxicity or antibody formation in individuals with spasticity or dystonia, and may enable treatment of more widespread spasticity [28]. The TOWER study (NCT01603459) investigated the safety and efficacy of incobotulinumtoxinA for spasticity due to cerebral causes in adults who required multi-pattern, unilateral treatment of both upper and lower limbs with total body doses of up to 800 U in a single injection cycle [27]. Results showed that titration of incobotulinumtoxinA, from the currently approved total upper-limb dose of up to 400 U in the United States [29] to a total dose of up to 800 U, allowed for effective treatment of a greater number of clinical patterns based on individuals' goals and needs, without compromising safety or tolerability. The study found no increased incidence of adverse events with escalating total body doses and repeat injections, and no new safety concerns were identified [27].

Given the burden of lower-limb spasticity and the paucity of data supporting the efficacy of BoNT treatment and functional improvements in this indication, this post-hoc analysis of the TOWER study assessed the efficacy of incobotulinumtoxinA for treating adult lower-limb spasticity, including pes equinovarus, in a sub-population of participants with post-stroke spasticity.

2. Materials and methods

2.1. Study design and participants

The TOWER study was a prospective, non-randomised, single-arm, multicentre, open-label, dose-titration study of individuals (18–80 years of age) with chronic upper- and lower-limb spasticity of the same body side due to cerebral causes, who were deemed by the investigator to require total body doses of incobotulinumtoxinA up to 800 U during the course of the trial [27]. Briefly, the study comprised 3 injection cycles with escalating, fixed total body doses of incobotulinumtoxinA (400, 600 and up to 800 U) injected in the same body side according to a target clinical pattern for treatment in all 3 injection cycles, selected by the investigator at screening to be pivotal to treatment success. Additional clinical patterns to be treated with the remaining dose of incobotulinumtoxinA were chosen at the investigators' discretion based on clinical need. The maximum dose per limb was 400 U in cycle 1, increasing to 600 U in cycles 2 and 3. In cycles 1 and 2, participants

could receive injections in the upper limb only, the lower limb only, or in both limbs, whereas in cycle 3, it was expected that most participants would receive injections in both limbs. The pre-defined dose range for treatment of pes equinovarus was 100–400 U.

This post-hoc analysis assessed the efficacy of incobotulinumtoxinA in a sub-population of participants from the TOWER study who had spasticity due to stroke, comparing those treated versus not treated in the lower limb.

2.2. Outcome measures

2.2.1. Resistance to passive movement

Lower-limb resistance to passive movement scale (REPAS) scores were assessed in participants who received lower-limb treatment (with or without upper-limb treatment) versus those who received upper-limb treatment only. All participants who were treated in the following lower-limb clinical patterns (with or without treatment in the upper limb) were classified as “treated in the lower limb”: flexed hip, adducted thigh, medially rotated hip, flexed knee, extended knee, pes equinovarus, pes equinovalgus, extended hallux and flexed toes (see Supplemental Table 1 for a list of muscles that could be treated in each clinical pattern). All other participants were classified as “treated in the upper limb only”.

The five REPAS items for the lower limb of the treated body side (movements: hip external rotation, knee flexion, knee extension, foot eversion/pronation, foot dorsiflexion) were rated using the AS [from 0 (no increase in muscle tone) to 4 (limb rigid in flexion or extension) [30]], resulting in a summed score from 0 to 20 [27,31].

2.2.2. Ashworth Scale

The change in Ashworth Scale (AS) score for the ankle joint was assessed in all participants who received treatment for the pattern pes equinovarus, as indicated by the investigator on the case report form and classified as “treated for pes equinovarus”, versus those who received treatment for other lower-limb patterns and/or upper-limb treatment only. Pes equinovarus AS was defined as the maximum of AS scores for foot supinators and plantar flexors. The selection of muscles and incobotulinumtoxinA dose was at the discretion of the investigator. Muscles treated for pes equinovarus could include medial gastrocnemius, lateral gastrocnemius, soleus, tibialis posterior, tibialis anterior, flexor hallucis longus and flexor digitorum longus. All other participants were classified as “not treated for pes equinovarus”, including those treated in the upper limb only and/or other lower-limb patterns. Additional muscles that could be treated and included in the AS scores for the ankle joint included peroneus brevis and peroneus longus (Supplemental Table 1).

2.2.3. Functional ambulation

Functional ambulation classification (FAC) scale scores were assessed in all participants who received at least one incobotulinumtoxinA treatment. The FAC scale was used to assess the independence and ambulation abilities of participants: from level 0 (no functional ambulation) to level 5 (ambulatory-independent) at baseline (injection), at 4-week post-treatment visits in each injection cycle, and at the end-of-study/end-of-cycle 3 visit (12–16 weeks post-treatment in cycle 3). The frequency of FAC scale scores over injection cycles was assessed.

2.2.4. Goal attainment for the lower limb

Goal attainment scale (GAS) scores for the lower limb were assessed as described previously [27,33] at each injection visit or at the end-of-study/end-of-cycle 3 visit in all participants who received lower-limb treatment. The number achieving 0, 1 or 2 of a possible 2 lower-limb goals in each injection cycle was reported.

2.3. Statistical analyses

Within each treatment group, changes in the lower-limb REPAS scores and ankle joint AS scores between injection cycle baseline and the 4-week post-treatment visit in each injection cycle are described with mean (SD). The effect of lower-limb treatment on changes in lower-limb REPAS scores and pes equinovarus treatment on the changes in ankle joint AS scores were assessed with analysis of covariance (ANCOVA), with the corresponding lower-limb REPAS value or ankle joint AS value at injection cycle baseline as the covariate. The effect of the lower-limb or pes equinovarus dose was assessed with multiple regression, with lower-limb dose and lower-limb REPAS score or pes equinovarus dose and ankle joint AS score at injection cycle baseline as independent variables. All analyses were descriptive.

AS responder rates (the proportion of participants with ≥ 1 -point reduction [improvement] in AS score for the ankle joint [32]) were compared by a Cochran–Mantel–Haenszel test, adjusting for the corresponding AS value at cycle baseline. FAC and GAS scores were analysed with frequency tables and descriptive summary statistics.

2.4. Ethics

These data were collected as part of the TOWER study; the participants gave their consent for ancillary studies. The investigators of the TOWER study also agreed to use of these data in ancillary studies. The TOWER study was registered at ClinicalTrials.gov (NCT01603459) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol, informed consent forms and other appropriate study-related documents were reviewed and approved by the local independent ethics committees and institutional review boards. All participants provided written informed consent [27].

3. Results

3.1. Participants

Of the 155 participants enrolled in the TOWER study, 132 (85%) had spasticity due to stroke. In this sub-population of participants with post-stroke spasticity, the mean (SD) age was 55.9 (12.0) years, and most (91/132, 69%) were male. All participants presented multifocal spasticity of the upper and lower limbs.

The distribution of limbs treated at each injection cycle is summarised in Table 1. Most participants received treatment in both the upper and lower limbs, with the proportion increasing from 67% in cycle 1 to 91% in cycle 2 and 98% in cycle 3 (Table 1).

In cycle 1, 99 participants were treated in the lower limb with a mean (SD) total limb incobotulinumtoxinA dose of 189.2 (99.2) U. In cycles 2 and 3, 119 and 121 participants were treated in the lower limb with mean (SD) total limb incobotulinumtoxinA doses of 257.1 (115.0) U and 321.3 (129.2) U, respectively. All lower-limb patterns treated at each injection cycle are summarised in Table 2. Consistent with increasing incobotulinumtoxinA dose, the number of lower-limb clinical patterns treated increased from 143 in cycle 1 to 203 in cycle 2 and 238 in cycle 3 (Table 2).

Investigators most frequently chose target clinical patterns in the upper limb for continuous treatment, with lower-limb patterns chosen for only 38/132 (29%) participants. However, pes equinovarus was the most frequently treated lower-limb clinical pattern in all cycles (Table 2) and was chosen as the target clinical pattern for continuous treatment in all 3 injection cycles in 30 participants. A total of 80 participants were treated for pes equinovarus in cycle 1, 105 in cycle 2 and 107 in cycle 3 (Table 2), with mean (SD)

Table 1

Distribution of limbs treated with incobotulinumtoxinA, and treatment of pes equinovarus, by injection cycle.

Injection cycle	Patients, n (%)
Cycle 1; N = 132	
Limbs treated	
Upper limb only	33 (25)
Both upper and lower limb	88 (67)
Lower limb only	11 (8)
Treated for pes equinovarus	
Yes	80 (61)
No	52 (39)
Cycle 2; N = 130	
Limbs treated	
Upper limb only	11 (8)
Both upper and lower limb	118 (91)
Lower limb only	1 (1)
Treated for pes equinovarus	
Yes	105 (81)
No	25 (19)
Cycle 3; N = 123	
Limbs treated	
Upper limb only	2 (2)
Both upper and lower limb	121 (98)
Lower limb only	0 (0)
Treated for pes equinovarus	
Yes	107 (87)
No	16 (13)

incobotulinumtoxinA doses of 177.1 (91.4) U, 215.1 (97.6) U and 251.5 (95.1) U, respectively. The muscles treated for pes equinovarus and doses administered at each injection cycle are detailed in Supplemental Table 2.

3.2. Muscle tone and resistance to passive movement

All injection cycles showed improvements (reductions) in REPAS lower-limb score from baseline to the 4-week post-treatment visit in participants treated in the lower limb. The mean (SD) improvements were -1.6 (2.1) in cycle 1, -1.9 (1.9) in cycle 2 and -2.2 (2.2) in cycle 3 (Table 3). For those treated in the upper limb only, the corresponding mean (SD) changes in REPAS lower-limb score were -0.4 (1.4) in cycle 1, -0.6 (1.6) in cycle 2 and -1.0 (0.0) in cycle 3 (Table 3). The difference in REPAS lower-limb score improvement between those treated in the lower limb and those treated in the upper limb only was significant in cycles 1 and 2 ($P = 0.0005$ and $P = 0.0133$; ANCOVA). Similarly, significant dose-dependent effects were noted for cycle 1 ($P = 0.0176$; multiple regression, Table 3). In cycle 3, only 2 participants were not treated in the lower limb.

The frequencies of change in AS score from study baseline to 4 weeks post-treatment in all injection cycles are shown in Fig. 1. Among those with data available for analysis, in all injection cycles, the responder rate was higher for participants treated

Table 2

Lower-limb clinical patterns treated with incobotulinumtoxinA.

Clinical pattern ^a	Patients treated for clinical pattern, n (%)		
	Cycle 1 (N = 132)	Cycle 2 (N = 130)	Cycle 3 (N = 123)
Flexed hip	0 (0)	0 (0)	6 (5)
Adducted thigh	3 (2)	4 (3)	5 (4)
Medially rotated hip	1 (1)	2 (2)	3 (2)
Flexed knee	11 (8)	21 (16)	27 (22)
Extended knee	10 (8)	20 (15)	24 (20)
Pes equinovarus	80 (61)	105 (81)	107 (87)
Pes equinovalgus	4 (3)	8 (6)	7 (6)
Extended hallux	10 (8)	10 (8)	20 (16)
Flexed toes	24 (18)	33 (25)	39 (32)

^a Patients could receive injections in > 1 site in each injection cycle.

Table 3
Change in REPAS lower-limb score and in AS score for the ankle joint.

	REPAS LL score at cycle baseline	REPAS LL score at 4 weeks post-treatment	Change in REPAS LL score	Between-group difference	Effect of dose
	Mean (SD)	Mean (SD)	Mean (SD)	<i>P</i> -value ^a	<i>P</i> -value ^b
Cycle 1					
Treated in lower limb (<i>n</i> = 99)	8.5 (2.8)	6.8 (2.9)	-1.6 (2.1)	0.0005	0.0176
Treated in upper limb only (<i>n</i> = 33)	9.0 (3.1)	8.6 (3.0)	-0.4 (1.4)		
Cycle 2					
Treated in lower limb (<i>n</i> = 118)	8.3 (3.0) ^c	6.4 (3.2)	-1.9 (1.9)	0.0133	0.1583
Treated in upper limb only (<i>n</i> = 11)	9.5 (2.5)	8.9 (2.5)	-0.6 (1.6)		
Cycle 3					
Treated in lower limb (<i>n</i> = 120)	7.9 (3.1) ^d	5.7 (3.1)	-2.2 (2.2)	0.3581	0.3258
Treated in upper limb only (<i>n</i> = 2)	8.5 (2.1)	7.5 (2.1)	-1.0 (0.0)		
	AS score at cycle baseline	AS score at 4 weeks post-treatment	Change in AS score	Between-group difference	Effect of dose
	Mean (SD)	Mean (SD)	Mean (SD)	<i>P</i> -value ^e	<i>P</i> -value ^f
Cycle 1					
Treated for pes equinovarus (<i>n</i> = 80)	2.75 (0.75)	2.08 (0.92)	-0.68 (0.79)	0.0099	0.0462
Not treated for pes equinovarus (<i>n</i> = 52)	2.48 (0.83)	2.21 (1.07)	-0.27 (0.72)		
Cycle 2					
Treated for pes equinovarus (<i>n</i> = 104)	2.64 (0.81) ^g	1.90 (0.96)	-0.74 (0.84)	0.255	0.01
Not treated for pes equinovarus (<i>n</i> = 25)	2.28 (1.02)	1.88 (0.93)	-0.40 (0.91)		
Cycle 3					
Treated for pes equinovarus (<i>n</i> = 106)	2.47 (0.85) ^h	1.62 (0.93)	-0.85 (0.78)	0.9621	0.5627
Not treated for pes equinovarus (<i>n</i> = 16)	1.94 (1.00)	1.25 (0.93)	-0.69 (0.70)		

Reductions in REPAS lower-limb score and AS score for the ankle joint represent improvement. ANCOVA: analysis of covariance; ANOVA: analysis of variance; AS: Ashworth Scale; LL: lower limb; *n*: number of observations; REPAS: resistance to passive movement scale.

^a *P*-value based on ANCOVA (with the corresponding REPAS cycle baseline value as covariate) for the between-group difference in change in REPAS lower-limb score comparing patients treated for the lower-limb clinical patterns flexed hip, adducted thigh, medially rotated hip, flexed knee, extended knee, pes equinovarus, pes equinovaglus, extended hallux and flexed toes with those treated in the upper limb only.

^b *P*-value based on multiple regression (with dose and the corresponding REPAS cycle baseline value as independent variables) for the effect of dose on the change in REPAS lower-limb score from injection cycle baseline to 4 weeks post-treatment.

^c *n* = 119.

^d *n* = 121.

^e *P*-value based on ANCOVA (with the corresponding AS cycle baseline value as covariate) for the between-group difference in change in AS score for the ankle joint, comparing patients treated for pes equinovarus (with or without treatment in the upper limb) with those not treated for pes equinovarus (including those treated in the upper limb and/or for other lower-limb patterns).

^f *P*-value based on multiple regression (with dose and the corresponding AS cycle baseline value as independent variables) for the effect of dose on the change in AS score for the ankle joint from injection cycle baseline to 4 weeks post-treatment.

^g *n* = 105.

^h *n* = 107.

versus not treated for pes equinovarus: cycle 1, 59% (47/80) versus 21% (11/52); cycle 2, 58% (60/104) versus 40% (10/25); cycle 3, 67% (71/106) versus 56% (9/16). The between-group difference was significant in cycle 1 ($P < 0.0001$; Cochran–Mantel–Haenszel test).

For participants treated and not treated for pes equinovarus, the mean (SD) baseline AS scores for the ankle joint were 2.75 (0.75) and 2.48 (0.83), respectively, in cycle 1; 2.64 (0.81) and 2.28 (1.02) in cycle 2; 2.47 (0.85) and 1.94 (1.00) in cycle 3 (Table 3). In all 3 injection cycles, mean changes in AS score for the ankle joint were greater for participants treated versus not treated for pes equinovarus: -0.68 versus -0.27 in cycle 1; -0.74 versus -0.40 in cycle 2; -0.85 versus -0.69 in cycle 3 (Table 3). For cycle 1, the between-group difference was significant ($P = 0.0099$; ANCOVA) and significant dose-dependent effects were noted for cycles 1 and 2 ($P = 0.0462$ and $P = 0.0100$; multiple regression, Table 3). In cycles 2 and 3, only 25 and 16 participants, respectively, were not treated for pes equinovarus.

3.3. Functional ambulation

In total, 60/132 (45%) participants had an FAC scale score of 4 at study baseline. FAC scale scores improved from study baseline to 4 weeks post-treatment in each injection cycle (Supplemental Table 3). The proportion of ambulator-independent participants (FAC scale score = 5) increased from 23% (31/132) at study baseline to 42% (51/121) at the end of cycle 3 (Fig. 2 and Supplemental Table 3).

3.4. Goal attainment for the lower limb

We found a consistent increase in goal achievement with repeated lower-limb treatment across injection cycles. At the end of cycles 1, 2 and 3, the number of participants achieving 2 of a possible 2 lower-limb treatment goals was 45/132 (34%), 63/130 (49%) and 78/123 (63%), respectively (Supplemental Table 4).

4. Discussion

Post-hoc analysis of TOWER study data showed that incobotulinumtoxinA treatment of the lower limb resulted in improvements in muscle tone after 4 weeks in participants with post-stroke spasticity who received treatment for chronic upper- and lower-limb spasticity of the same body side due to cerebral causes. Specifically, lower-limb treatment was associated with improvements in REPAS lower-limb score, and treatment for pes equinovarus was associated with improvements in AS score for the ankle joint. In addition, for the first time, we show that incobotulinumtoxinA treatment in the TOWER study resulted in improvements in FAC scale scores, with the percentage of participants able to walk independently at the end of cycle 3 almost double that at study baseline. Goal attainment also increased consistently with repeated incobotulinumtoxinA treatment, with 63% of participants achieving 2 (of 2) lower-limb

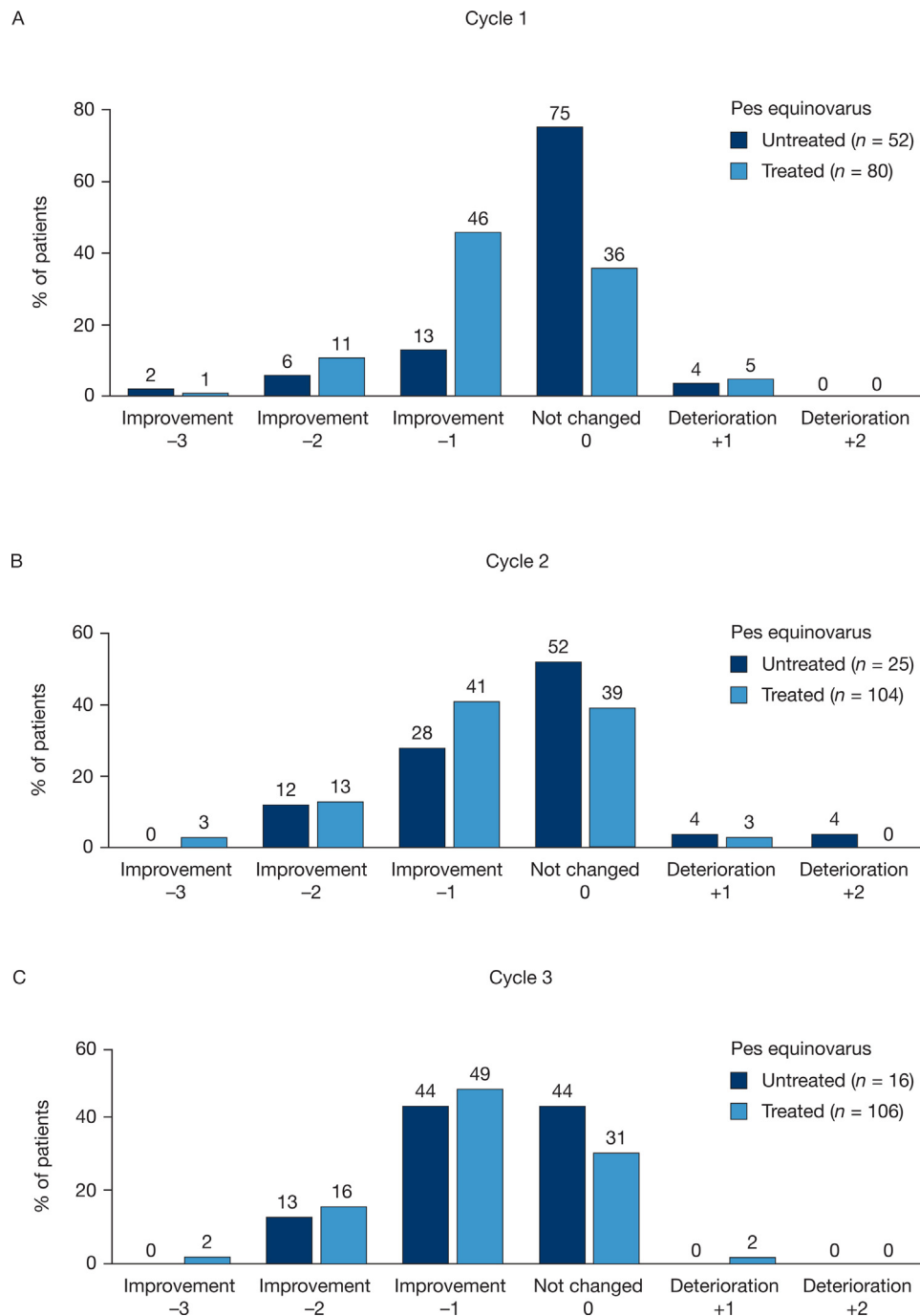


Fig. 1. Change in Ashworth Scale score (4-point scale) for the ankle joint from baseline to 4 weeks post-treatment with incobotulinumtoxinA in A. cycle 1, B. cycle 2 and C. cycle 3. Responders were classed as participants with ≥ 1 -point reduction (improvement) in Ashworth Scale scores from injection cycle baseline to 4 weeks post-treatment.

treatment goals at the end of cycle 3, which underlines the benefit of the clinical approach.

Data showing the impact of BoNT on lower-limb spasticity are scarce, but our data for improvements in ankle joint AS score with lower-limb treatment are consistent with results of a previous placebo-controlled study of onabotulinumtoxinA for post-stroke lower-limb spasticity [4]. In this previous study, onabotulinumtoxinA treatment resulted in a significantly greater reduction in ankle joint muscle tone (MAS) from baseline to weeks 4, 6 and 8 post-treatment in the onabotulinumtoxinA group versus placebo recipients, accompanied by a clear improvement in the investigator's Clinical Global Impression score, both assessed as secondary

endpoints [4]. Similar results have also been shown for the treatment of lower-limb spasticity in other placebo-controlled studies [20,22,24]. In a recent placebo-controlled study of abobotulinumtoxinA with open-label extension, lower-limb treatment with doses of abobotulinumtoxinA 1500 U resulted in significant improvement in muscle tone (MAS) of the gastrocnemius–soleus complex versus placebo at 4 weeks post-treatment [23]. Following repeated treatments with abobotulinumtoxinA 1000 U or 1500 U (depending on clinical need) in the extension period, participants experienced stabilisation of muscle tone improvements [23].

Combined upper- and lower-limb treatment may further optimise results. Treatment in the upper limb alone can influence

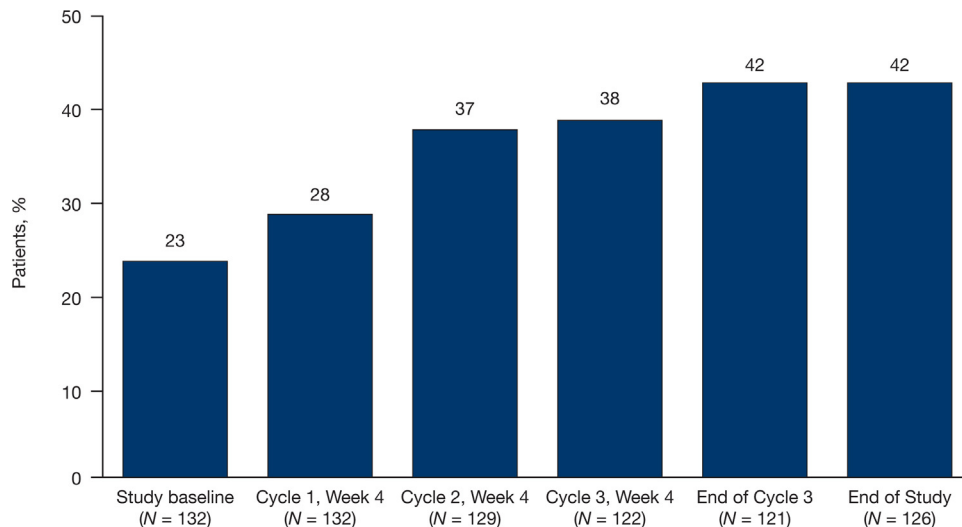


Fig. 2. Proportion of participants with Functional Ambulation Classification scale score = 5 (ambulator-independent). N: number of observations.

gait and has been shown to improve impairments associated with lower-limb spasticity [34]. Furthermore, BoNT treatment can modulate other positive features of upper motor-neuron syndrome, such as clonus [35], disturbed reciprocal inhibition/activation [36] and posture [34]. Of note, in a recent real-world study, 24% of individuals receiving upper-limb BoNT treatment selected improved gait and balance as a therapeutic goal [37]. Most participants in the TOWER study received both upper- and lower-limb treatment for chronic spasticity post-stroke [27] and greater improvements in muscle tone were observed in those treated versus not treated in the lower limb or for pes equinovarus. This finding highlights the potential efficacy of incobotulinumtoxinA for treating lower-limb spasticity and the added benefit of treating lower-limb clinical patterns in individuals with multi-focal upper- and lower-limb spasticity. Consistent with this, rather than deterioration of motor function and increased disability that may be expected in individuals with chronic post-stroke spasticity [1,2,38], analysis of the functional effects of treatment in the TOWER study population revealed a large proportion of participants with a FAC score of 5 who were able to walk independently after repeated incobotulinumtoxinA treatment.

The TOWER study was a prospective, open-label dose titration study primarily designed to investigate the safety of escalating incobotulinumtoxinA doses for treating both upper- and lower-limb spasticity in as many clinical patterns as was necessary and possible. As such, this post-hoc analysis was limited by the low number of participants not treated in selected clinical patterns in comparator groups. In cycle 3, only 2 participants were not treated in the lower limb. Furthermore, in cycles 2 and 3, only 25 and 16 participants, respectively, were not treated for pes equinovarus. These population sizes resulted in low power for the statistical tests and did not allow for meaningful analysis of REPAS and AS, respectively. The analysis of AS and REPAS scores on a linear scale may be viewed as a further limitation of this analysis. Although the AS (and MAS) is an ordinal scale, it is often analysed as a linear variable with mean changes presented and is an accepted measure of spasticity improvement [29,39]. With a paucity of well-designed clinical trials, data showing the functional benefit of lower-limb BoNT treatment are lacking and are so far inconclusive [25]. The results of the current study highlight the potential benefit of lower-limb incobotulinumtoxinA treatment for improving active functioning and warrant further research.

5. Conclusions

In this study, incobotulinumtoxinA showed efficacy for treating pes equinovarus and other patterns of lower-limb spasticity in participants with post-stroke spasticity receiving treatment for lower-limb spasticity with or without treatment in the upper limb.

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Disclosure of interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.rehab.2020.03.005>.

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