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Review

Does botulinum toxin treatment improve upper limb active function?

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ABSTRACT

Background: Spasticity following lesions of the central nervous system such as stroke is a major cause of impairment and disability, especially when it affects the upper limb, and can be focally relieved by intramuscular injections of botulinum toxin (BT). Functional improvements of the affected upper limb after a BT focal treatment remain controversial.
Objective: We aimed to assess the functional effects of BT treatment on upper-limb spasticity in the literature, identify flaws and deficiencies in proving these effects and propose leads for future trials.
Methods: We searched the MEDLINE and Cochrane databases for trials, reviews and meta-analyses assessing the effect of BT injection in upper-limb spasticity. This was a non-systematic narrative review, and the selection of articles was based on the authors' expertise. The review focused on stroke-related spasticity and disability.
Results: Patients' therapeutic targets involved use of the disability assessment scale (DAS) or goal attainment scale (GAS). Impairments and passive function goals prevailed for active function and participation and were more frequently achieved for the former than the latter. Meta-analyses showed no to mild effect sizes for improvement in upper-limb function but failed to show higher and/or better use of the paretic upper limb in activities of daily living after BT injection.
Conclusion: BT injections for impairment and passive function are related to improved kinematic parameters; however, the relation between relief of spasticity and improved upper-limb activity has not been established. Possible explanations for the lack of functional effect in studies are first, disability is mainly due to muscle weakness rather than spasticity, so patients with the best underlying motricity may benefit the most from BT injections; second, assessment methods may not be adapted to screen eligible patients; third, most studies' endpoints were at 4 to 12 weeks after a single injection, but repeated treatment sessions might be needed to observe functional outcome on the upper limbs; and finally, the association of rehabilitation programs or non-pharmacological treatments may enhance the functional effects of BT injections.

1. Introduction

Spasticity is a distressing positive feature of upper motor-neuron syndrome (UMNS), which results from the disruption of the corticospinal tract after lesions of the central nervous system [1,2]. Etiologies are diverse, such as stroke, multiple sclerosis, traumatic brain and spinal cord injury and cerebral palsy [2]. Spasticity is characterized by an increased stretch-reflex activity and its severity ranges from a mild stretch reflex to sustained hypertonia and permanent contracture. Pandyan defines it as "disordered sensori-motor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles". In its broadest sense, this definition includes all positive signs of UMNS [1] and represents a major cause of impairment and disability, especially when it affects the upper limb [1].

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For almost 30 years, botulinum toxin A (BoNT-A), derived from a neurotoxin synthesized by *Clostridium botulinum* that blocks the pre-synaptic release of acetylcholine at the motor plate level, has been used in focal intramuscular injections to diminish muscle contraction and selectively treat spasticity [3,4]. Its efficacy on stroke-related upper-limb spasticity (ULS) impairments has been well demonstrated [5–7], but whether BoNT-A significantly improves upper-limb function is still debated. Many physicians and researchers have tried to link the decreased spasticity to functional improvements, with heterogeneous results [8–10].

This open debate among the physical medicine and rehabilitation community raises the following question: are clinical trials assessing the functional effects of BoNT-A for treating ULS really designed to show a positive effect on upper-limb active function? We aimed to answer this question by reviewing the main published trials and meta-analyses of studies of BoNT-A in ULS. First, we review how patients' goals and priorities are set, then how functional outcomes have been assessed to date. Finally, we discuss why BoNT-A injection has not been found functionally effective and provide leads on how future studies should be designed to demonstrate the efficacy of local BoNT-A injections on active use and participation of upper limbs.

2. Methodological considerations

This study is a narrative non-systematic review of literature. The selection of articles was based on the authors' expertise. Systematic reviews and meta-analyses assessing the efficacy of BoNT-A injections in ULS were searched in the MEDLINE/PubMed and Cochrane databases up to October 2017 by using the MeSH terms "spasticity", "upper limb", "botulinum toxin". Relevant reports of randomized controlled trials (RCTs) and *princeps* studies were also critically reviewed. Of note, the available literature on ULS treatment mainly concerned stroke-related symptoms and impairments in the adult population. We excluded isolated case reports, small case series and cohorts for other etiologies of ULS.

The following sections are based on a review of 8 systematic reviews (with or without meta-analysis) and 18 clinical trials and studies.

3. Goals for the treatment of ULS

Before considering the target population and the timing to start with focal treatments for ULS, the functional outcomes and how they have been evaluated so far seems necessary. Sheean proposed dichotomising passive and active functions as:

- tasks that are carried out on the affected limb by the unaffected one or by caregivers;
- an active use of the paretic limb during daily activities [8].

With this distinction, the analysis of the heterogeneity of "functional outcomes" in previously published clinical trials is simpler.

Different scales and outcome measures were identified by Ashford and Turner-Stokes in a systematic review of the literature [11]. Among 411 identified studies, 22 assessed passive or active function with 3 main approaches:

- patients' self-reported items mainly concerned hand hygiene, ease in putting arms in sleeves and cutting fingernails [12]. These items were grossly similar to the Disability Assessment Scale (DAS) [13,14]. Although the DAS has strength as a well-validated scale for assessing the impact of spasticity and its treatment, it assesses more impairments (pain, limb position, hygiene) or activities that can be a passive function (e.g., dressing a sleeve) than upper-limb active function;
- use by the same team of a composite measure of function that combined an Ashworth score for elbow, wrist and fingers; 3 items of the Barthel index (dressing, feeding and grooming); and 3 other functional items (cutting fingernails, cleaning palms and putting the arm through a garment sleeve) [12,15]. Although interesting, this approach combined symptoms and functional scores and validated and non-validated items, which induced statistical flaws such as interpretation and analysis biases;
- the Goal Attainment Scaling (GAS) was used in only 2 RCTs [12,16]. In this approach, in agreement with the medical team, patients define goals to achieve with the studied intervention. The expected target is set at the value of 0. Outcomes achieved less than expected are rated −2 or −1 and those achieved more than expected, +1 or +2. The GAS allows for calculating a T-score and the interindividual comparison of treatment efficacy among patients with different therapeutic goals [17]. The interpretation of the GAS results requires classifying patients' goals according to the World Health Organization International Classification of Functioning, Disability and Health (ICF) matching domains, to differentiate impairment/symptoms or activities and participation targets.

The main therapeutic goals/patient priorities, according to the DAS or GAS approaches are in Table 1.

In 2002, Brashear et al. used the DAS domains they developed and validated, and before treatment start, asked participants to choose their principal target of treatment [13]. In following studies, Kanovsky et al. [18,19] and Barnes et al. [20] used the same methods to evaluate patient-centred efficacy. The authors showed a similar distribution of patients' main therapeutic targets. Hence, dressing (ease for caregivers or active participation in) was the main goal identified by post-stroke patients at more than 4 years after onset of ULS. Limb position and hygiene remained important, 20 to 36% of patients defining them as a primary therapeutic target. Pain was a relatively minor goal in these trials. In patients with long-lasting spasticity, limb position (which is a passive goal) accounted for two thirds of main therapeutic target in study population. In all 3 studies, the ULS scheme was similar.

The GAS was used as a secondary outcome in 2 RCTs, by Bakheit et al. in 2001 [15] (data not presented in the article) and McCrory et al. in 2009 [16] (with ancillary analyses by Turner-Stokes et al. in 2010 [21]). Second, Turner-Stokes et al. developed multicentre studies that investigated the main goals for ULS treatment by using the GAS [22–24]. They summed their results in goal areas by using the ICF as follows: first, "impairment", "symptoms" or "body function"; second, "passive function" mostly meaning "ease of care"; then "active function", including active use (assessed by Ashford's Arm Activity scale [25,26]), self-care or domestic tasks, and mobility (transfers, gait, balance). In these studies, passive goals (impairment and passive function) are more represented than active use and function as primary goals for ULS treatment by BoNT-A injection after stroke.

4. Functional outcomes of focal treatment of ULS

Three pharmacological formulations of BoNT-A are routinely administered for treating ULS. The toxins onabotulinum (Botox®, Allergan Inc., Irvine, CA, USA), abobotulinum (Dysport®, IPSEN, Paris, France) and incobotulinum (Xeomin®, Merz Pharma GmbH., Frankfurt, Germany) have proven their efficacy for spasticity in large RCTs [12,13,15,18,27–30]. Undoubtedly, BoNT-A is an effective treatment for symptoms and impairments by reducing muscle tone, improving range of motion, and decreasing related

Table 1
Main therapeutic goals and proportion of patients choosing them as a primary target, at initiation of treatment of upper-limb spasticity with botulinum toxin injection.

Study	Patients and methods	Therapeutic goals	Goal preferences, *n* (%)	Efficacy results
Brashear et al., 2002	DAS *n* = 126 patients (RCT, 64 in BoNT-A vs 62 in control group) Cause of spasticity: stroke Mean time since onset = 4.75 years	Dressing Limb position Hygiene Pain	40 (31.7) 38 (30.2) 33 (26.2) 15 (11.9)	≥ 1 point improvement in the principal treatment target: 62 vs 27% in controls (*P* = .007)
Kanovsky et al., 2009 and 2011	DAS *n* = 148 participants Cause of spasticity: Stroke Mean time since onset = 55.0 months	Dressing Limb position Hygiene Pain	60 (40.5) 54 (36.5) 30 (20.3) 5 (3.4)	Significant improvement in dressing, position and hygiene at 2, 4 and 8 weeks compared to placebo. Superiority of BTI at 2 and 4 weeks for pain
Barnes et al., 2010	DAS *n* = 192 participants Cause of spasticity: Stroke (88%), TBI (5.7%), CP (1.6%), MS (0.5%) Mean time since onset = 75.0 months	Limb position Dressing Hygiene Pain	63.0% 23.6% 7.9% 5.5%	For primary target, 51 patients (63%) were responders in the 20 U/mL group vs 44 (52%) in the 50 U/mL group
Turner-Stokes et al., 2010	GAS *n* = 90 participants Cause of spasticity: stroke Mean time since onset = 5.9 years	No. of goals = 165 Impairment/body function Upper limb activities Mobility Self-care tasks Domestic tasks	46 (28) 30 (18) 11 (7) 57 (34) 21 (13)	Not assessed
Turner-Stokes et al., 2013	GAS *n* = 456 participants Cause of spasticity: stroke Mean time since onset = 61.4 months	Passive function (ease of care) Impairment (muscle tone, ROM etc.) Active function Pain Involuntary movements Mobility Other ICF domains	132 (29.0) 105 (23.0) 104 (22.8) 61 (13.4) 41 (9.0) 10 (2.2) 3 (0.7)	Achievement rates 85.6% 78.1% 72.1% 83.6% 78.0% 70.0% 100%
Ashford et al., 2016	GAS *n* = 696 goals Review of 4 studies by the same team	Symptoms/impairments Pain Involuntary movements ROM/contractures/deformity Passive function Active function Active use and domestic tasks Mobility (transfers, gait, balance) Therapy facilitation	315 (45) 78 (11) 75 (11) 162 (23) 242 (35) 132 (19) 120 (17) 11 (2) 8 (1)	Not assessed
Gracies et al., 2016	DAS *n* = 238 participants Causes of spasticity: stroke (*n* = 215; 90%), traumatic brain injury (*n* = 23; 10%) Mean time since onset = stroke, 5 years; TBI, 10 years	Limb position Dressing Hygiene Pain	108 (45) 63 (27) 51 (21) 15 (6)	Achievement rate for primary treatment target: At week 4–62.0% in Abo1000 group, 50.0% in Abo500, 39.2% in placebo Achievement of limb position goal as PTT: At week 4–50.6% in Abo1000 group, 36.3% in Abo500, 29.1 in placebo

BoNT-A: botulinum toxin A; DAS: disability assessment scale; GAS: goal attainment scale; CP: cerebral palsy; MS: multiple sclerosis; ROM: range of motion; TBI: traumatic brain injury; ICF: WHO International Classification of Functioning, Disability and Health

pain and discomfort. As mentioned before, some studies used measurements such as the DAS and GAS that partially investigated the functional outcome of focal treatment of ULS.

To date, the largest RCT included 333 participants and compared the efficacy of BoNT-A injection combined with an evidence-based therapy program to therapy alone [28]. This trial failed to show any significant improvement in upper-limb active function assessed by the 1-month Action Research Arm Test (ARAT), as a primary outcome. Basic upper-limb functional activities such as dressing a sleeve, cutting fingernails and palmar hygiene significantly improved at 1 and 3 months with BoNT-A injection ($P = 0.017$, $P = 0.047$ and $P = 0.045$, respectively), but these activities can be considered passive (i.e., performed by a caregiver) or active function. There was no effect on the ability to use cutlery, which was the only truly active function outcome.

Similar results were obtained by Brashear et al. in 2002 [13] in 126 patients (64 in the BoNT-A group, 62 in placebo). At 6 weeks, 83% with BoNT-A injection experienced at least a 1-point improvement in one or more domains of the DAS as compared with 53% with placebo and 62 versus 27% experienced improvement in their principal target of treatment ($P < 0.0001$ and $P = 0.007$, respectively) (Table 1). Global assessments by physicians and patients/caregivers were correlated with the 6-week DAS score.

Finally, both studies by Kanovsky et al. [18,19] showed the same superiority of incobotulinum toxin over placebo on the DAS, after a single administration and for repeated injections. Of note, primary goals on the DAS mainly concerned passive upper-limb function and had the higher achievement rate (Table 1).

Recently, the Upper Limb International Spasticity Study (ULIS) group published the results of the ULIS-II trial [22,23], which intended to reflect more real-life treatment and to evaluate the achievement of primary therapeutic targets defined by the GAS, after one cycle of BoNT-A. Passive function (goals regarding ease of care) and impairments (muscle tone, range of motion, limb position) were the 2 most frequent goal areas set by patients as a

primary target. They were also the most achieved, along with pain, in 85.6%, 78.1% and 83.6% of patients, respectively. Active function and mobility were less achieved, with rates of 72.1 and 70% (Table 1). When defined as secondary goals, the achievement rate of active function targets dropped to 60.3% of patients. This finding was previously demonstrated in the ancillary analysis of GAS outcomes from McCrory et al. [16]. Passive function targets are more often achieved than are active function targets, defined as primary or secondary goals [21].

We specifically reviewed 3 meta-analyses that focused on the functional outcome of BoNT-A for treating ULS (Table 2). Francis et al. developed an interesting paradigm to correlate decreased spasticity with functional improvement over time. Although spasticity decreased and functional improvement were significantly associated with low to moderate doses of onabotulinum toxin, the authors found no relation between these changes over time. Patients in the high-dose group did not experience functional improvement even though spasticity decreased significantly. Recently, Foley et al. [6] and Baker and Pereira [31,32] showed a slight improvement in active function of the upper limb with BoNT-A injection but with significant heterogeneity and small to moderate effect size. Furthermore, these effects did not translate into an increased use of the paretic upper limb in activities of daily living. Baker and Pereira also showed that the reviewed trials had an overall "very low" grade of evidence.

5. How to evaluate functional outcome for ULS focal treatments?

In light of these results, it seems that focal treatment of ULS with BoNT-A intramuscular injections alleviates spasticity-related impairments (muscle tone, active and passive range of motion) and abilities or performance of the paretic upper limb. However, patients' self-defined therapeutic targets are mostly passive function. Furthermore, when comparing passive and active goals, the latter are much less achieved than are the first [21]. Finally,

Table 2
Functional outcomes and results from reviews and meta-analysis of BoNT-A in upper-limb spasticity (ULS).

Study reference	Reviewed studies and methods	Results	Synthesis
Francis et al., 2004	2 RCTs–142 patients (complete data for 137) BoNT-A: Onabotulinum toxin "Composite spasticity index" (sum of MAS [0–5] for elbow, wrist and finger flexors), range [0–15] "Composite functional index" (sum of items 3,5,8 of the Barthel index, and 3 other subjective assessments: cutting fingernails, cleaning palm, putting arm through sleeve), range [0–17] Primary endpoint 4 weeks post-injection Secondary endpoints 8, 12 and 16 weeks post-injection	No improvement: $n=10$ Spasticity reduction alone: $n=31$ Function improvement alone: $n=5$ Both improved: $n=91$ Time relationship between spasticity and function changes: $T_{spasticity}=T_{function}$: $n=47$ $T_{spasticity}<T_{function}$: $n=26$ $T_{function}<T_{spasticity}$: $n=18$ In placebo group: no association between spasticity and function changes ($P=0.1775$) In 500 U group: spasticity reduction associated with function improvement ($P=0.0090$) In 1000 U group: spasticity reduction associated with function improvement ($P=0.0018$) In 1500 U group: no association between spasticity and function changes ($P=0.6393$)	For low to moderate doses of onabotulinum toxin, there is an association between spasticity reduction and function improvement There is no temporal relationship between spasticity and functional changes Functional outcome measure is not validated
Foley et al., 2013	16 studies Meta-analysis: pooled data from 10 trials, ie. 1000 patients Studies criteria: (1) RCT; (2) adult population, >60% post-stroke ULS; (3) comparison to placebo or non-pharmacologic treatment; (4) assessment of activity performance Scales and scores used as functional outcomes: Barthel, FIM, MAL (amount of use and quality of movement), ARAT, Klein-Bell ADL, 9-hole peg, upper-limb activity questionnaire	Individual analysis: Improvement in upper-limb activity outcomes: $n=6$ Decrease in functional outcome: $n=8$ Not reported: $n=2$ Results pooled by similarity of outcome: DAS improvement in treated group ($P<0.0001$) ARAT improvement ($P=0.013$) Pooled treatment effects with standardized mean differences (independent from the outcome measurement used): Range [−2.379; 1.511] Pooled SMD = 0.536 ± 0.094, 95% CI [0.352; 0.721], $P<0.0001$	BoNT-A treatment of ULS results in both deterioration and improvement of upper-limb activity Outcome measures are heterogenous Effect size was moderately in favor of BoNT-A
Baker and Pereira 2016	18 studies Outcome measures: Active range of motion (AROM): $n=8$ ARAT; $n=3$ Barthel index: $n=7$ Other measurements (individual studies): Rivermead motor assessment, 9-hole peg, FIM, MAL, Wolf Motor Function Test Primary endpoints: 4 to 12 weeks	Results of individual outcome measures: At 4 to 12 weeks AROM: MD = 4.53, 95% CI [2.43; 6.64], $P<0.0001$ ARAT: MD = 1.86, 95% CI [0.52; 3.19], $P=0.006$ Barthel: MD = 2.16, 95% CI [0.74; 5.07], $P=0.14$ Pooled analysis with standardized mean differences: Including Barthel index, SMD = 0.31, 95% CI [0.00; 0.62] $P=0.05$; heterogeneity, I2 = 76% Excluding Barthel index, SMD = 0.32, 95% CI [0.01; 0.62] $P=0.04$; heterogeneity, $I^2=49\%$	Regarding grades of evidence, studies assessing upper-limb function after BoNT-A were all "very low" Pooled analysis was slightly positive regarding active upper-limb function, with very small size of effect, and significant heterogeneity These results do not seem to reflect a better and/or increased use of the paretic limb in ADL

ADL: activities of daily living; ARAT: action research arm test; AROM: active range of movement; DAS: disability assessment scale; FIM: functional independence measurement; MAL: motor activity log; MAS: modified Ashworth scale; MD: mean difference; RCT: randomized controlled trial; SMD: standardized mean difference.

meta-analyses do not show an improvement in active participation and overall independence.

Here, we discuss 4 hypotheses to explain why the positive effects of BoNT-A on impairments and abilities do not translate into active functional outcomes. First, muscle weakness prevails on spasticity in causing disability, so patients with the best underlying motricity may benefit the most from BoNT-A injections. Second, assessment methods may not be adapted to screen eligible patients; third, the time of assessment at 4 to 12 weeks after a single injection may not be sufficient to show significant functional improvement, and finally, targeted rehabilitation programs should be considered along with BoNT-A treatment to enhance upper-limb active function.

5.1. Spasticity and underlying motricity

Several authors have tried to correlate the degree of spasticity with functional performance, thereby showing a link between the direct effect of BoNT-A on muscle tone and functional benefits for hemiparetic patients [8,9,33,34]. Sheean tried to define the past methodological flaws and clinical considerations to improve upcoming clinical trials [8], and Bensmail et al. developed an interesting approach by studying the kinematics of ULS, before and after BoNT-A injections [33,34]. The authors showed that some parameters improved with BoNT-A injection, allowing for smoother and quicker movements in achieving tasks performed at a comfortable speed [33]. They also found that the "amount-of-use" subscore of the motor activity log (MAL) scale increased by 10 points after 2 sessions of BoNT-A injections [34]. Unfortunately, this finding failed to reach statistical significance and also for the correlation between changes in kinematic parameters and changes in functional scores. Finally, the authors identified a subpopulation of patients who benefited the most from toxin injections: those with good proximal motor control and moderate distal control, along with moderate MAL scores at baseline [34]. From these results, there might be a functional benefit of BoNT-A injection in less disabled patients. Thus, BoNT-A injections may improve some kinematic parameters and reaching–grasping abilities, but we still have no evidence of a link between treating spasticity and improving upper-limb active function, in terms of participation in activities of daily living.

5.2. Assessment tools and study design

The modified Ashworth scale was the primary endpoint used in most RCTs. This endpoint induced sample selection bias, favouring the recruitment of the most spastic patients with the most severe underlying motor impairment. These patients have few capacities of functional improvement.

The MAL reflects the everyday use of the upper limb in post-stroke patients and might be the most reliable clinical tool for the assessment of functional effects of BoNT-A in ULS, for less disabled patients. Only 2 studies investigated the effect of BoNT-A in terms of MAL [35,36]. In both studies, BoNT-A injections (or placebo in the Meythaler et al. study) were associated with a standardized program of physical therapy. Chang et al. compared the effects of BoNT-A with that of therapy between 9 participants with high hand function and 5 with low-hand function, assessed by the Chedoke McMaster Assessment [35]. The MAL-28 scores were higher at 12 weeks ($P = .006$) in the higher hand-function than lower hand-function group. Moreover, changes in MAL-28 (+25%), MAL-5 (+25%) and MAL self-reporting scales (+89%) over time (12 weeks) were significant in the entire cohort. Finally, changes in the MAL-5 over time were significantly higher ($P = .02$) in the higher hand-function than lower hand-function group. All these findings suggest that BoNT-A would have a clear functional effect on ULS but also that chronic post-stroke patients with better hand function at baseline would benefit the most from the association of BoNT-A and physical therapy [35]. The small number of participants, the non-controlled design of the study and the lack of correlation analysis between impairment, grasping ability (MAS and ARAT) and functional outcome do not allow for generalizing these results. Therefore, they open the field for larger RCTs assessing functional outcome for focal treatment of ULS.

In addition, the EXCITE trial [37] was the first to identify the pre-treatment MAL score as a meaningful predictor of constraint-induced movement therapy (CIMT) efficacy. A MAL-quality of movement (MAL-QOM) score of ≥ 2 (/5) predicted a good outcome (MAL-QOM ≥ 3 at 2 weeks and 12 months) for CIMT. Only patients with partially preserved pre-treatment UL function benefitted the most from CIMT. Similar to the EXCITE trial, future studies of BoNT-A treatment in ULS should focus on patients with partially preserved UL function, assessed with adapted methodological tools.

5.3. Combined rehabilitation programs

The Cochrane stroke group published a meta-analysis by Demetrios et al. that did not find good evidence for the effectiveness of multidisciplinary rehabilitation after BoNT-A injections [38]. However, too few studies have assessed combined pharmacological and physical therapies for ULS with a sufficient assessment time period to confirm (or reject) the hypothesis of a functional benefit of BoNT-A treatment in ULS.

According to the Bensmail et al. and Park et al. studies [33,34,37], patients included in future RCTs should be selected on the basis of the underlying motor control of their upper limb and its quality of use (i.e., proximal Medical Research Council [MRC] score for muscle strength assessment $> 3/5$, distal MRC score $> 2/5$ and MAL-QOM score $\geq 2/5$). Furthermore, results from the Chang et al., Meythaler et al. and Demetrios et al. studies [35,36,38] invite assessing, on a larger scale, the impact of a combined intervention in a proper crossover study. Such trials could assess the functional outcome of a focal treatment for ULS, combining impairment, target goals and functional use of the spastic paretic upper limb with the MAL scale used as a screening and primary outcome measure. The crossover design would help define a strategy of combined therapy and injections, one potentiating the other. Repeated BoNT-A injections and an extended time for a functional primary endpoint should also be considered.

6. Synthesis and prospects

Our literature review revealed that BoNT-A injections in the upper limbs for post-stroke spasticity are efficient to reduce impairments (hypertonia, pain, limb position, range of motion) and to achieve passive function targets, allowing for mostly better ease of care (hand hygiene, passive dressing, etc.). First, these improvements result in greater comfort and decrease fatigue, without significant improvement in daily use of the upper limb, in patients overall and in those most disabled. Second and most important, these improvements are linked to better kinematic parameters – reaching and grasping abilities in a specific subset of less disabled patients (with moderate to good underlying motor control). Nonetheless, the relation between spasticity and upper-limb activity has not been established. The primary negative features of pyramidal tract lesions are well known to prevail in the resulting disability. Future studies should help physicians better identify patients who could have the best functional benefits from intramuscular injections of BoNT-A in terms of the amount and quality of use of the spastic upper limb in activities of daily living. RCTs are needed to assess the functional outcomes of BoNT-A

injections, as part of a multidisciplinary strategy, in post-stroke upper-limb spasticity, among a pre-selected subset of patients. These trials should focus on patients with moderate levels of motor impairment (proximal MRC score ≥ 3 and distal MRC $\leq 2/5$), because they may benefit the most from reduced muscle hypertonia in performing activities of daily living. The ARAT, Wolf Motor Function Test and MAL scale could serve as screening and inclusion criteria as well as primary outcome measures, combined with the GAS and/or activities of daily living.

7. Conclusion

We lack evidence of a direct functional benefit of reducing muscle overactivity with focal treatment of upper-limb spasticity with BoNT-A injections, because the motor impairment may largely prevail upon spasticity in causing disability after a pyramidal tract lesion. Patients hampered by disabling spasticity but whose underlying motor control remains satisfactory may expect a true improvement in active use. A better screening of these patients, adapted evaluation tools, repeated injections and a protocol combining BoNT-A injection with rehabilitation programs may help refine prior results and demonstrate functional outcomes.

Disclosure of interest

Jonathan Levy has received honoraria from Merz Pharma for medical consulting, and has been invited to congresses and seminars by Merz Pharma, Allergan and Ipsen. Thibaud Lansaman has been invited to congresses and seminars by Merz Pharma, Allergan and Ipsen. Djamel Bensmail has perceived honoraria for medical consulting, been invited to congresses and seminars, from Merz Pharma, Allergan and Ipsen. Franco Molteni, Giovanni Cannaviello, Nicolas Roche declare that they have no competing interest.

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