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REVIEW ARTICLE

Botulinum Toxin Type A for the Treatment of Lower Limb Spasticity after Stroke

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Abstract

Post-stroke lower limb spasticity impairs balance and gait leading to reduced walking speed, often increasing wheelchair use and caregiver burden. Several studies have shown that appropriate treatments for lower limb spasticity after stroke include injections of botulinum toxin type A (BoNT-A), phenol or alcohol, surgical correction and a rehabilitation program. In the present article, we review the safety and effectiveness of BoNT-A for the treatment of lower limb spasticity after stroke, with a focus on higher doses of BoNT-A. The cumulative body of evidence coming from the randomized clinical trials and open-label studies selected in the article suggest BoNT-A to be safe and efficacious in reducing lower limb spasticity after stroke. Studies of high doses of BoNT-A also showed a greater reduction of severe post-stroke spasticity. In stroke survivors with spasticity of the ankle plantar-flexor muscles, a combined approach between surgery and BoNT-A can be indicated. However, controversy remains about improvement in motor function relative to post-stroke spasticity reduction after BoNT-A treatment.

1 Introduction

Botulinum toxin type A (BoNT-A) has been recommended as a first-choice treatment for focal upper and lower limb spasticity in several European consensus statements and by the American Academy of Neurology [1, 2]. However, it is difficult to prove its effectiveness especially in terms of functional benefit, and controversy exists about possible increased motor function correlated to an improvement in spasticity [3].

Lower limb spasticity after stroke reduces stability and impairs gait and walking speed, increasing the need for orthosis, wheelchair, and caregiver assistance. A correct clinical assessment and identification of treatment objectives are necessary to inform treatment choice. Therefore, an interdisciplinary approach, including physical medicine and rehabilitation specialists, neurosurgeons and orthopedic surgeons, is required to optimize treatment [4]. In subjects with lower limb spasticity after stroke, the spasticity pattern usually involves knee extensor muscles, producing a clinical

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Key Points

After stroke, different muscles are responsible for spastic equinus foot; a careful clinical evaluation and an interdisciplinary approach is therefore required for optimal administration of botulinum toxin type A (BoNT-A) therapy.

In stroke survivors, it is important to differentiate between spasticity and weakness in leg muscles prior to treatment with BoNT-A.

Studies of high doses of BoNT-A showed a greater reduction of severe spasticity after stroke.

In stroke survivors with spasticity in the plantar-flexor muscles, a combined approach between surgery and BoNT-A should be considered.

picture of "stiff knee", and ankle plantar-flexor muscles producing a prolonged abnormal posture of equinovarus foot. Sometimes adducted foot (strephenopodia) at rest or during the gait cycle is seen, with an overactive tibialis posterior muscle. Many muscles are responsible for spastic equinus foot (e.g. medial and lateral gastrocnemius, soleus, tibialis posterior, flexor hallucis longus and brevis, flexor digitorum longus and brevis, and extensor hallucis brevis), but given that gastrocnemius and soleus are most frequently involved in this typical pattern, BoNT-A treatment targets these muscles to reduce the drive to plantar flexion [4, 5]. In particular, treatment is directed to the spasticity causing the equinus deformity as well as the mechanical defect, and the aim of treatment is to allow the whole foot to be in contact with the ground during stance phase—thus acting as a stable platform—so the muscles controlling the hip and knee can ensure movement is effectively controlled [5]. Recently, there has been renewed interest in improving gait function. For stroke patients, overactivity of leg extensor muscles may help support their body, standing position and stance phase of gait cycle, but may also interfere with knee flexion during the swing phase [6, 7]. In this situation, it may be useful to reduce stiff knee due to knee extensor spasticity (rectus femoris or vastus intermedius) with BoNT-A injections or orthopedic surgery.

The main goal of rehabilitation in these patients is the reduction of hypertonia, and many approaches are available even if BoNT-A combined with adjunctive therapies (casting, taping, or orthosis) is proposed as the first choice for focal spasticity [8–10]. BoNT-A reduces spasticity in selected muscles by blocking acetylcholine release at the neuromuscular junction [1, 2]. The effect lasts about 3–4 months. The temporary reduction of muscle tone allows physical and occupational therapy, such as muscle strengthening and facilitation, increasing articular range of motion (ROM), retraining of ambulation and gait, and the fitment of orthosis—thus improving function in the activities of daily living.

Difficulties in showing improvement of motor function relative to the spasticity reduction following BoNT treatment have been reported, especially for upper limb impairment—in which both weakness and spasticity of wrist and finger flexor muscles reduce the capacity for hand movement in stroke survivors. Conversely, BoNT-A therapy for lower limb spasticity not only increases the articular passive ROM related to spasticity reduction, as occurs also in the upper limbs, but it can also improve the heel contact at ground, stability, and speed of gait. For these reasons, several outcome measures have been used in studies to show the effect on gait function after BoNT-A injections in stroke survivors treated for lower limb spasticity, i.e. 10-meter walk test (10MWT) [11], 2- or 6-min walk test (2MWT or 6MWT) [12] and timed up and go test (TUG test) [13]. The objective of the present article was to review the current evidence on the safety and effectiveness of BoNT-A therapy for post-stroke lower limb spasticity, with a particular focus on higher doses.

2 Literature Search Strategy

In the present review article, we included English language reports from the international literature published from January 1989 to December 2017, reviewing randomized placebo-controlled (RCTs), double-blind and open-label trials, and existing meta-analyses that provided a description of the employment of BoNT-A for the treatment of lower limb spasticity after stroke. This review was based upon searches of US National Library of Medicine (PubMed), Ovid MEDLINE, EMBASE, Google Scholar, Web of Science, and Scopus databases using the term "botulinum toxin type A" combined with "lower limb spasticity", "post-stroke spasticity", "upper and lower limb spasticity", and "spasticity and gait". The references of each study selected were screened to identify studies that were not included by electronic search. Key textbooks were also searched. We did not include congress abstracts/posters, articles that were not peer-reviewed, or case-reports. Studies were included if: (1) subjects had experienced lower limb spasticity for identified ischemic or hemorrhagic stroke; (2) BoNT-A was injected to any spastic lower limb muscle; (3) the sample size included four or more subjects; (4) the intervention applied was BoNT-A alone or combined with adjunctive therapies; (5) spasticity reduction was the main objective of the study; (6) BoNT-A dose was in international units (U) and not in nanograms (Ng). We considered studies using different techniques [ultrasound, electrical stimulation or electromyography (EMG) guided]

for BoNT-A injection. Participants who had received BoNT-A treatment were compared with those who had received control-placebo and/or usual care such as other drugs, physiotherapy or surgery. We did not evaluate studies comparing adjunctive therapies after BoNT injection. Finally, we did not include studies in which the origin of spasticity was not clearly indicated to be stroke (i.e. we did not consider spastic hemiparesis due to non-stroke CNS conditions). From 224 articles identified, we screened titles and abstracts of the citations, identifying 89 articles for closer review. Ultimately, by excluding another 52 articles that did not meet inclusion criteria, we obtained full copies of the 37 potentially suitable reports for further assessment. After inclusion of 2 articles of interest from the reference lists of the selected articles and exclusion of other 9 articles, 30 studies met our eligibility criteria and were included in the overall review (Tables 1, 2 and 3).

3 Licensed Indications for the Commercial Preparations of Botulinum Toxin Type A in Post-stroke Spasticity

Since 1989, the effectiveness of BoNT-A in reducing spasticity after stroke has been demonstrated with reversibility and low prevalence of complications, obtaining the approval of U.S. Food and Drug Administration and European regulatory agencies for this indication [2, 14, 15]. At present, in USA and Europe, three formulations of BoNT-A are commercially available and used in clinical practice: onabotulinumtoxinA (Botox®, Allergan, Inc., USA), abobotulinumtoxinA (Dysport®, Ipsen, France), incobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals GmbH, Germany). The preparations are manufactured by different processes, with various formulations and potencies, which are determined by diverse biological assays based on their clinical use [16].

There are different licensed indications for the three marketed BoNT-A preparations in post-stroke spasticity. In Europe and USA, onabotulinumtoxinA can be used for wrist, fingers, ankle, and toe spasticity, incobotulinumtoxinA for upper limb spasticity, and abobotulinumtoxinA for upper and lower limb spasticity in Europe and only upper extremity in USA [15, 17]. Several studies demonstrated no difference in potency between onabotulinumtoxinA and incobotulinumtoxinA [18, 19]. However, the conversion ratios between abobotulinumtoxinA and incobotulinumtoxinA or onabotulinumtoxinA are not yet clear. It has been supposed that 100 U of onabotulinumtoxinA or incobotulinumtoxinA are bioequivalent to 300 U of abobotulinumtoxinA [16, 20]. Another difference between the three BoNT-A products involves their protein structure: onabotulinumtoxinA and abobotulinumtoxinA formulations have the neurotoxin associated to a larger protein complex containing accessory proteins, whereas incobotulinumtoxinA formulation presents a neurotoxin purified, free from complexing proteins with a high specific biological activity [21]. The absence of accessory proteins could be responsible for a reduced risk of developing anti-drug antibodies, but this hypothesis has not yet been proven.

4 Botulinum Toxin Type A for the Treatment of Lower Limb Post-stroke Spasticity

4.1 Botulinum Toxin Type A for Ankle Plantar-flexor Muscle Spasticity

Various RCTs and open-label studies evaluated the effectiveness of BoNT-A in reducing ankle plantar-flexor spasticity after stroke [22–34] (Table 1). Among RCTs [22–28], two Phase III trials showed significant reductions of Modified Ashworth Scale (MAS) score in subjects treated with 100 U onabotulinumtoxinA (onabotulinumtoxinA, − 0.8; placebo, − 0.6) [22] and 1500 U abobotulinumtoxinA [23] during the double-blind phase. For both trials, the patients who completed the double-blind phase entered an open-label phase with additional treatments (≤ 400 U of onabotulinumtoxinA) [22] or the same dosage (1000 U or 1500 U abobotulinumtoxinA) [23] at ≥ 12-week intervals. Across all treatment cycles, the incidence of adverse effects related to treatment was 8.5% (39/457), decreasing with each treatment cycle for one trial [22] while there were two deaths (1 pulmonary embolism, 1 "natural causes", both on placebo), generalized muscular weakness and dysphagia induced by 1500 U abobotulinumtoxinA due to remote toxin spread for the other RCT [23] (Table 1). In another double-blind RCT, stroke survivors were treated in four groups (abobotulinumtoxinA 500 U, 1000 U, 1500 U, and placebo), and a MAS score reduction for ankle plantar-flexor muscles for the treatment and control groups throughout the 12-week study period was reported [24]. However, the subjects treated with 1500 U BoNT-A showed the greatest reduction in spasticity versus those receiving placebo after 1, 2, and 3 months. The distance walked in 2 min increased significantly in all treatment groups, but there was no statistically significant difference between groups. Surprisingly, with a baseline in excess of 90 m, little or no change was found in groups treated with 1000 U or 1500 U abobotulinumtoxinA or with placebo, whereas in the group receiving 500 U abobotulinumtoxinA a greater change was observed (approximately 10 m) [24] (Table 1).

In another double-blind RCT, a significantly greater decrease from baseline in the MAS ankle score was noted at Weeks 4, 6, and 8 in the onabotulinumtoxinA group (300 U) compared to the placebo group [25]. Moreover, a significantly greater increase in the Clinician Global Impression

Table 1 Key and reviewed studies on botulinum toxin type A (BoNT-A) in the treatment of spasticity of ankle plantar-flexor muscles and other selected muscles after stroke

First author and year of publication	Study design	Objective of the study	Patients characteristics and outcome measures	Dose (U)	Muscles injected/injection guide	Efficacy outcomes/adverse effects
Wein et al. 2018 [22]	Multicenter, randomized, double blind, placebo-controlled trial	To investigate the efficacy and safety of onaBoNT-A in ankle spasticity	447 chronic stroke patients MAS, CGI, GAS, and pain scale	100 U onaBoNT-A placebo	SOL, GM, GL, TP Others ES, EMG, and US guidance	Improvement in symptoms and in ankle muscle tone as early as week 2 after a single treatment, along with significant improvements in function compared to placebo; consistent improvement with repeated treatments over 1 year with higher doses
Gracies et al. 2017 [23]	Randomized, double-blind, placebo-controlled, single-cycle multicenter trial	To assess the effectiveness of aboBoNT-A on spasticity, function, and safety	331 chronic stroke patients MAS for ankle plantar-flexor muscles, comfortable barefoot walking speed, and PGA	1000 U aboBoNT-A; 1500 U aboBoNT-A; placebo	SOL, GM, GL Others ES guidance	Consistent efficacy in tone and functional parameters with a high safety profile
Pittock et al. 2003 [24]	Double-blind, randomized, placebo-controlled	To assess the efficacy of three different doses of aboBoNT-A	234 chronic stroke patients 2MWT, step length, stepping rate, RMA, MAS for ankle plantar-flexor, passive ROM of ankle, subjective assessment of pain in the knee, leg, ankle or foot (0–3)	500 U; 1000 U; 1500 U aboBoNT-A; placebo	GM, GL, SOL Palpation guidance	MAS reduction of ankle plantar flexor muscles in all groups during the study period and greatest reduction in spasticity in 1500 u aboBoNT-A group. Improvement in 2MWT in all groups including placebo
Kaji R et al. 2010 [25]	Double-blind, randomized, parallel group, placebo-controlled	To assess the efficacy and safety of one set injections of aboBoNT-A	120 chronic stroke patients MAS for ankle plantar-flexor gait pattern, speed of gait, CGI	300 U aboBoNT-A placebo	GM, GL, SOL, TP	A significantly greater decrease in the MAS ankle score in treatment group. Similar increase in CGI score. No significant differences in gait patterns and speed. No adverse events

Table 1 (continued)

First author and year of publication	Study design	Objective of the study	Patients characteristics and outcome measures	Dose (U)	Muscles injected/injection guide	Efficacy outcomes/adverse effects
Burbaud et al. 1996 [26]	Crossover, randomized, placebo-controlled study	To assess the effectiveness of aboBoNT-A compared to placebo	23 chronic stroke patients AS for ankle plantar-flexor FMA; subjective efficacy (0-3)	1000 U total aboBoNT-A placebo	GM, GL, SOL, TP, FDL EMG guidance	Significant improvement in plantar-flexor and invertor muscles AS compared to placebo; subjective improvement in foot spasticity after BoNT-A but not after placebo. Slight improvement in gait velocity
Johnson et al. 2014 [27]	Non-blinded randomized controlled trial	To investigate the effect of combined BoNT-A and FES treatment on spastic drop foot	18 chronic stroke patients Walking speed, Physiological Cost Index, MAS, RMA, and Medical Outcomes Study 36-Item Short-Form Health Survey	200 U (GM, GL) 400 U (PT) aboBoNT-A	GM, GL, TP EMG guidance	Statistically significant improvement in walking speed and function in BoNT-A added with FES group compared to control and BoNT-A alone over 12 weeks
Dunne et al. 2012 [28]	Double-blind randomized placebo-controlled trial, open-label extension phase	To examine safety and efficacy onaBoNT-A on plantar-flexor overactivity	85 chronic stroke patients AS for plantar-flexor muscles, adverse events, self-reported spasm frequency, VAS, physician rating of hypertonia severity, gait quality, and active dorsiflexion	200 U 300 U onaBoNT-A placebo	TP, SOL, FDL, GM EMG/ES guidance	No differences between groups at 12 weeks. At least one point in AS reduction for patients with AS > 3 compared to placebo. Significantly greater improvement in spasm frequency, pain reduction, active dorsiflexion, gait quality after BoNT-A injections
Hesse et al. 1994 [29]	Observational study	To elucidate the effects of BoNT-A treatment on lower limb extensor spasticity	10 chronic stroke patients; AS for plantar-flexor muscles, RMA (leg/trunk), and kinesiological measurements during gait	400 U onaBoNT-A	SOL, TP, GM, GL EMG guidance	AS reduction in all subjects. Statistically significant improvement in gait analysis parameters (velocity, stride length, stance symmetry) and in the length of the force point of action under the affected foot

Table 1 (continued)

First author and year of publication	Study design	Objective of the study	Patients characteristics and outcome measures	Dose (U)	Muscles injected/injection guide	Efficacy outcomes/adverse effects
Santamato et al. 2013 [30]	Prospective, open-label study	To assess safety and efficacy of incoBoNT-A on equinus-varus deformity	71 chronic stroke patients MAS score for plantar-flexor muscles, PADFM, and SFS	≤ 180 U (25-100 in single muscle) incoBoNT-A	GM, GL, SOL US guidance	Statistically significant MAS and SFS scores reduction one and three months after injection and increase of passive ankle dorsi-flexion motion one and three months after treatment. Mild adverse events reported by 8 patients
Mancini et al. 2005 [31]	Randomized, double-blind, dose-ranging study	To outline beneficial and unwanted effects of three different BoNT-A doses in the treatment of spastic foot	45 chronic stroke patients MAS, MRC, gait assessment, Achilles tendon clonus, VAS for Gait Function and Pain, and Adverse Effects Scale	167 U (median) 322 U (median) 540 U (median) onaBoNT-A	GM, GL, TP, SOL EMG guidance	Significant scale scores improvement after treatment with BoNT-A, especially in those with a median dose higher. Adverse effects were found in subject treated with the highest dose (prolonged weakness of the treated limb, flu-like syndrome and edema of the injected leg)
Pimentel et al. 2013 [32]	Randomized, prospective, double-blind trial.	To evaluate the effect of BoNT-A (higher vs lower doses) on spasticity and function	21 chronic stroke patients MAS for plantar-flexor muscles, 10MWT, and FIM motor score	300 U 100 U onaBoNT-A	GM, GL, SOL Palpation guidance	Significant improvement in spasticity in higher-dose group, improvement in 10MWT, FIM motor score in both groups but with no significance
Picelli et al. 2012 [33]	Cohort study	To investigate the relationship between GM echo intensity and response to BoNT-A	56 chronic stroke patients Heckmatt scale, MAS, TS, and ankle passive ROM	500 U total aboBoNT-A	GM, GL US guidance	Significant improvements after 4 weeks in spastic gastrocnemius. No significant change in the echo muscle intensity of the spastic gastrocnemius after BoNT-A injection. Clinical outcomes significantly better in Heckmatt II compared to III and IV

Table 1 (continued)

First author and year of publication	Study design	Objective of the study	Patients characteristics and outcome measures	Dose (U)	Muscles injected/injection guide	Efficacy outcomes/adverse effects
Picelli et al. 2014 [34]	Randomized controlled trial	To compare the clinical outcomes of manual needle placement, ES, and US guided techniques for BoNT-A injection into the spastic GM	47 chronic stroke patients MAS, TS, and ankle passive ROM	200 U total onaBoNT-A	GM, GL ES, manual, and US guidance	Better improvement in US group at MAS plantarflexors after one month. Greater improvement in passive dorsiflexion in US group compared to electrical stimulation and manual needle placement. No difference between groups for the TS
Tok et al. 2012 [35]	Placebo-controlled, non-randomized trial	To compare the efficacy of BoNT-A in RF compared to placebo in stiff knee gait	25 chronic stroke patients gait analysis, energy expenditure, 10-m and 6-min walk tests, MAS rectus femoris	100–125 U onaBoNT-A	RF ES guidance	Significant improvement in knee flexion during swing phase and a reduction in energy cost. Spasticity reduction in RF, improvement in knee kinematics and functional assessment at two months better then placebo
Roche et al. 2015 [36]	Prospective observational study	To determine how gait modification affects response to BoNT-A in RF spasticity	22 chronic stroke patients MAS and gait analysis parameters	150–200 U onaBoNT-A	RF ES guidance	Spontaneous gait speed significantly increased after BoNT-A injection; the percentage increase in peak knee flexion in swing during fast gait before injection is a useful predictor of the increase in peak knee flexion following RF BoNT-A injection
Hameau et al. 2014 [37]	Before-after trial	To assess the effect of BoNT-A on RF on both the stretch reflex and voluntary strength	14 chronic stroke patients 10-MWT (fast and spontaneous), 6-MWT, TUG, time to ascend stairs, and time to descend stairs	164 ± 49 U onaBoNT-A	RF ES guidance	Spasticity reduction; reduction of peak knee extensor torque; peak knee flexor torque increased during maximal concentric and isometric contraction after injection. No changes in functional test

Table 1 (continued)

First author and year of publication	Study design	Objective of the study	Patients characteristics and outcome measures	Dose (U)	Muscles injected/injection guide	Efficacy outcomes/adverse effects
Caty et al. 1998 [41]	Observational study	To study the effect of BoNT-A on stiff knee gait (RF vs several muscles)	20 chronic stroke patients AS, Duncan-Ely test, Stroke Impairment Assessment Set, gait analysis, ABILOCO and 10-MWT, SATI-SPART-Stroke and 36-item Short-Form Health Survey	100–200 U onaBoNT-A	RF, ST, GM, GL, SOL, triceps surae ES/EMG guidance	Improvement in Stroke Impairment Assessment Set. Reduced spasticity of RF and; increased knee flexion during the swing phase, lower energetic cost. Unchanged participation and quality of life
Rousseaux et al. 2014 [42]	Open label observational study	To investigate the efficacy of injections on this flexor scheme	9 chronic stroke patients, MAS, passive ROM, MRC, and VAS for difficulties	300–400 U onaBoNT-A	Iliopsoas, knee flexors, RF, ST, SM, BF, hip adductors, hip rotators, GM, SOL ES guidance	Modest improvement in hip and knee extension at MAS and better extension passive movements, better limb positioning. No changes in active functions
Yelnik et al. 2003 [43]	Case series	To explore the efficacy of BoNT-A for EHL overactivity.	11 chronic stroke patients EHL overactivity 4-point scale, pain (0-2), capacity to wear shoes, and heel varus deformity	66–100 U onaBoNT-A	EHL, TA, TP ES guidance	Improvement in pain, shoe difficulties and EHL overactivity remaining for more than 6 months in 4 patients
Supputtitada et al. 2002 [44]	Single-center, open-label, prospective study	To investigate the efficacy and safety of BoNT-A in stroke survivor spastic toes	14 chronic stroke patients MAS, visual pain scale, visual percentage of function scale, and adverse effects	25–35 U AS 2; 50–70 U AS 3; 75–95 U AS 4 onaBoNT-A	FDL, EHL, FHL EMG guidance	Improvements observed in all outcome measures lasting from 5-6 months to 2 years No adverse effects
Fietzek et al. 2014 [61]	Single-centere double-blind randomized placebo-controlled trial	To investigate the efficacy of BoNT-A to reduce ankle muscle hypertonia vs placebo	35 chronic stroke patients MAS	230 U total onaBoNT-A placebo	GM, GL, SOL, TP Anatomical guidance	MAS reduction in BoNT-A group compared to placebo at Week 12. In spastic feet receiving BoNT-A in the first cycle comparatively lower MAS scores over all follow-up data and at Week 24 than those treated with placebo and then with onaBoNT-A

Table 1 (continued)

First author and year of publication	Study design	Objective of the study	Patients characteristics and outcome measures	Dose (U)	Muscles injected/injection guide	Efficacy outcomes/adverse effects
Tao et al. 2015 [62]	Single-center Phase II randomized double-blind placebo-controlled pilot study	To establish the effect of low dose BoNT-A in subacute stroke patients	23 subacute stroke patients step length, cadence, speed, 6MWT,FMA of the lower limbs, MAS, EMG, and MBI	200 U total onaBoNT-A placebo	GM, GL, SOL, TP ES guidance	Improvement in gait analysis, FMA, MAS, MBI in BoNT-A group, and daily living abilities

aboBoNT-A abobotulinumtoxinA, *AS* Ashworth Scale, *BF* biceps femoris, *CGI* Clinical global impression, *DAS* Disability Assessment Scale, *EHL* extensor hallucis longus, *EMG* electromyography, *FDL* flexor digitorum longus, *FES* functional electric stimulation, *FHL* flexor hallucis longus, *FIM* functional independence measure, *FMA* Fugl-Meyer assessment, *GAS* goal attainment scale, *GL* gastrocnemius lateralis, *GM* gastrocnemius medialis, *incoBoNT-A* incobotulinumtoxinA, *MAS* modified Ashworth scale, *MBI* modified Barthel index, *MRC* Medical Research Council, *onaBoNT-A* onabotulinumtoxinA, *PADFM* passive dorsi-flexion grade of motion, *PGA* physician global assessment, *RF* rectus femoris, *RMA* Rivermead motor assessment, *ROM* range of motion, *SFS* spasm frequency scale, *SOL* soleus, *SM* semimembranosus, *ST* semitendinosus, *TA* tibialis anterior, *TP* tibialis posterior, *TS* Tardieu scale, *TUG* timed up and go, *U* units, *US* ultrasonography, *VAS* Visual Analogue Scale, *2MWT* 2-min walking test, *6MWT* 6-min walking test, *10MWT* 10-meter walk test

(CGI) score was reported by the investigator in the onabotulinumtoxinA group compared to the placebo group at Weeks 4, 6, and 8. Serious adverse events were reported in 9% (5/58) in the onabotulinumtoxinA group and 2% (1/62) in the placebo group during the 12-week follow-up period and all were resolved. All these events except for myalgia were considered to be unrelated to BoNT-A [25] (Table 1).

In two RCTs, stroke survivors treated with 1000 U abobotulinumtoxinA showed significant improvements in Ashworth Scale (AS) for plantar-flexor and invertor muscles compared to placebo 3 and 4 months after therapy [26], while reductions in AS and adverse event frequencies were no different between different onabotulinumtoxinA doses (300 U, 200 U and placebo) [28] (Table 1). However, 14/31 subjects with AS > 3 at baseline in the onabotulinumtoxinA group experienced a significant reduction of > 1 grade versus 1/17 following placebo. Overall, patients receiving onabotulinumtoxinA experienced significantly greater improvements in spasm frequency, pain, active dorsiflexion, and gait quality than controls [28]. AbobotulinumtoxinA also produced a significant subjective improvement in foot spasticity compared to placebo. In terms of functional effect, a slight but not significant improvement in gait velocity was revealed after BoNT-A [26] (Table 1). Finally, in a non-blinded RCT in 21 stroke survivors with equinus spastic foot, those treated with BoNT-A and functional electrical stimulation improved walking speed and function more than the control group or the group treated only with abobotulinumtoxinA over 12 weeks of follow-up [27] (Table 1). Therefore, the reviewed RCTs showed efficacy in reducing ankle plantar-flexor spasticity with different doses of onabotulinumtoxinA [22, 25] and abobotulinumtoxinA [23, 24, 26], combined with functional improvements [24–26, 28].

In clinical practice it is difficult to enroll spastic patients in a placebo group due to their high need for treatment, therefore many studies of BoNT-A therapy have been of open-label design. Among these reports, Hesse and colleagues observed that 400 U onabotulinumtoxinA injected under EMG guidance into soleus, tibialis posterior and both heads of gastrocnemius muscles, reduced ankle plantar-flexor spasticity measured with AS in 10 chronic stroke subjects, two weeks after the treatment [29]. Gait analysis showed a statistically significant improvement in velocity, stride length, stance symmetry, and the length of the force point of action under the affected foot. There were no systemic severe side effects. Two patients reported a slight weakness of the plantar flexion and knee extension [29] (Table 1). In another open-label study in 71 stroke survivors with equinovarus deformity, incobotulinumtoxinA at a maximum total dose of 180 U (range 25–100 U per muscle) reported a significant reduction in MAS and spasm frequency scores 30 days after treatment, lasting to 90 days of follow-up. Two weeks after treatment, eight patients reported adverse events (11%), all

Table 2 Key and reviewed studies on higher doses of abobotulinumtoxinA (aboBoNT-A, Dysport), onabotulinumtoxinA (onaBoNT-A, Botox), and incobotulinumtoxinA (incoBoNT-A, Xeomin) in the treatment of lower limb post-stroke adult spasticity

First author and year of publication	Study design	Objective of the study	Patient characteristics and outcome measures	Doses (U) for lower limb muscles	Lower limb muscles injected/ injection guide	Efficacy outcomes/ adverse effects
Baricich et al. 2015 [47] Hesse et al. 1995 [48]	Retrospective observational study Randomized non-placebo-controlled study	To evaluate the efficacy and safety of high doses of onaBoNT-A in upper and/or lower limb post-stroke spasticity To test the effect of BoNT-A in two groups patients with lower limb spasticity	26 chronic hemiparetic patients with upper and lower limb spasticity MAS, DAS, and GAE 6 chronic hemiparetic patients with lower limb spasticity AS, MRC, and cycle parameters	Mean thigh dose: 75,6 ± 21,3 U onaBoNT-A Mean leg dose: 404.4 ± 112.4 U onaBoNT-A 2000 U aboBoNT-A and ES	RF, ADDLBM, BF, GM, GL, SOL, TP, TA, FDL, FHL, and EHL US guidance GM, GL, SOL, and TP EMG guidance	Significant MAS reduction 30 and 90 days with functional improvement and no adverse events were reported MAS reduction with gait parameters improvement only in subjects treated with ES. Adverse effect in one subject: bladder paresis
Santamato et al. 2013 [49]	Prospective, nonrandomized, open-label study	To test the efficacy and safety of higher doses of BoNT-A in patients with upper and lower limb spasticity after stroke	25 patients with upper and lower limb spasticity AS, DAS, VAS, and GATR	Up to 340 U incoBoNT-A	RF, ADDLBM, BF, GM, GL, SOL, TP, TA, FDL, FHL, and EHL US guidance	Disability, pain and spasticity reduction 30 and 90 days after the injection, one patient reported injection site pain, four patients experienced muscular weakness
Santamato et al. 2017 [50]	Prospective, nonrandomized, open-label study	To test the long-term efficacy and safety of higher doses of BoNT-A in patients with post-stroke upper and lower limb spasticity	20 patients with upper and lower limb spasticity treated for 2 years AS, DAS, VAS, and GATR	Up to 460 U incoBoNT-A	RF, ADDLBM, BF, GM, GL, SOL, TP, TA, FDL, FHL, and EHL US guidance	Disability, pain and spasticity reduction 30 days after the eight set of injections and no severe adverse effects

ADDLBM adductor longus-brevis-magnus, *AS* Ashworth scale, *BF* biceps femoris, *BoNT-A* botulinum toxin type A, *DAS* disability assessment scale, *EHL* extensor hallucis longus, *EMG* electromyography, *ES* electrical stimulation, *FDL* flexor digitorum longus, *FHL* flexor hallucis longus, *GATR* global assessment of treatment response, *GAE* global assessment of efficacy, *GL* gastrocnemius lateralis, *GM* gastrocnemius medialis, *MAS* modified Ashworth scale, *MRC* Medical Research Council, *RF* rectus femoris, *SOL* soleus, *TA* tibialis anterior, *TP* tibialis posterior, *U* units, *US* ultrasonography, *VAS* visual analogue scale

Table 3 Reviewed studies of comparison between botulinum toxin type A (BoNT-A) and other therapies for the treatment of lower limb spasticity

First author and year of publication	Study design	Objective of the study	Patients characteristics and outcome measures	Dose (U)	Muscles injected/injection guide	Efficacy outcomes/adverse effects
Kirazli et al. 1998 [63]	Randomized, double-blind study	To compare BoNT-A and phenol in relieving ankle plantar flexor and foot invertor spasticity	20 chronic stroke patients AS	400 U total onaBoNT-A, 3 ml of 5% phenol	GM, GL, SOL, TP EMG guidance	At follow-up, significant improvement in AS for dorsiflexion in both groups. with reduction in eversion spasticity significant in botulinum group injection but not phenol
Rousseaux et al. 2008 [64]	Open-label study	To compare the effect of BoNT-A and tibial nerve neurotomy	34 chronic stroke patients MAS, ankle active ROM passive ROM, balance, FAC, gait velocity, step length, RMA	300 U onaBoNT-A	SOL, GM, GL, TP, TA, FHL, FDL ES guidance	Tibial nerve neurotomy was more effective than BoNT-A injection on most of the functional parameters
Bollens et al. 2013 [65]	First assessor-blinded, randomized, controlled trial	To compare the effect of BoNT-A and tibial selective nerve neurotomy	16 chronic stroke patients TS, MAS, MRC, 10MWT, ankle passive ROM	75-200 U onaBoNT-A	SOL, TP, FHL ES guidance	Comparable improvements of ankle kinematics during gait but higher reduction in ankle stiffness in neurotomy group compared to BoNT-A
Picelli et al. 2015 [66]	Pilot randomized controlled trial	To compare the effects of therapeutic US and TENS with BoNT-A in 3 groups (US, TENS tibial nerve, botulinum toxin)	30 chronic stroke patients MAS, ankle passive ROM	200 U onaBoNT-A	GM, GL US guidance	Significantly better ankle passive articular excursion in treatment group compared to those treated with physical therapies

AS Ashworth Scale, *EMG* electromyography, *ES* electrical stimulation, *FAC* functional ambulation categories, *FDL* flexor digitorum longus, *FHL* flexor hallucis longus, *GL* gastrocnemius lateralis, *GM* gastrocnemius medialis, *MAS* modified Ashworth scale, *MRC* Medical Research Council, *onaBoNT-A* onabotulinumtoxinA, *RMA* Rivermead motor assessment, *ROM* range of motion, *SOL* soleus, *TENS* Transcutaneous Electrical Nerve Stimulation, *TA* tibialis anterior, *TP* tibialis posterior, *U* units, *US* ultrasonography or ultrasound, *10MWT* 10-meter walk test

mild in intensity and rapidly resolving [30] (Table 1). The reviewed open-label studies thus supported the efficacy of onabotulinumtoxinA [29] and incobotulinumtoxinA [30], with improvements in functional effect.

Many studies have shown treatment of triceps surae muscles to improve gait and balance in subjects with lower limb spasticity [31–34], although with no agreement on optimal dose and injection technique. In particular, in a RCT in 45 subjects with spastic ankle plantar-flexor muscles allocated to onabotulinumtoxinA at a mean total dose of either 167 U, 322 U or 540 U, all doses produced significant improvement in scale scores, with the two higher doses showing greater and more prolonged responses than the lower dose [31]. The highest rate of side effects 4 weeks after treatment was seen at the highest dose. The middle dose (322 U spread over 2–5 muscles) was found to be best in producing long-lasting improvement of spastic foot dysfunction [31] (Table 1). On the other hand, Pimentel and colleagues found that functional improvements did not change with BoNT-A dose. In 11 stroke subjects receiving a total of 300 U onabotulinumtoxinA and 10 patients receiving 100 U using palpation and anatomic landmarks as guides [32], the higher dose produced a significantly greater reduction in MAS score after 8 and 12 weeks, whereas there were no significant differences between doses in 10MWT and Functional Independence Measure (FIM) motor score at any point. Therefore, the improvements in gait velocity and FIM motor score were not correlated to BoNT-A dose. Two patients experienced mild calf pain just after injection, resolving in 2–3 days [32] (Table 1).

Injection technique is key to maximizing precision and avoiding neurotoxin spread to other sites. Several recent studies have investigated using ultrasound guidance since it permits accurate observation of muscle size and characteristics such as structural changes like fatty infiltration and fibrous involution, which can reduce the effect of BoNT-A. Picelli and colleagues demonstrated in 56 stroke survivors that triceps surae muscles with spasticity of Heckmatt grades III or IV, had less tone reduction and less improvement in ankle passive ROM 4 weeks after 250 U abobotulinumtoxinA injected into each of the medial and lateral gastrocnemius muscles under ultrasound guidance, than subjects with spastic muscles of grades I or II [33] (Table 1). Furthermore, they compared three different techniques (anatomic landmarks and palpation, electrical stimulation, and ultrasound) for 100 U onabotulinumtoxinA injection into the gastrocnemius muscles of 47 stroke survivors with spastic equinus [34]. One month after injection, MAS improved more with ultrasonography than with anatomic landmarks and palpation. The ankle passive ROM improved more with ultrasonography than with either electrical stimulation or anatomic landmarks and palpation [34] (Table 1).

4.2 Botulinum Toxin Type A for Other Muscles of Lower Limb with Spasticity

Many studies have described BoNT-A therapy in several spastic muscles of the lower limb; however, in stroke survivors, the treatment of muscles other than ankle plantar-flexor muscles is not always licensed [35–37] (Table 1). There are many reasons for injecting other muscles. First, there is the stiff knee due to spasticity of rectus femoris or vastus intermedius muscles, which impedes leg flexion during the swing phase of gait and (together with a spastic equinus) causes asymmetry in hemiplegic gait. Injection of spastic leg extensor muscles may reduce this impairment, as well as the release of rectus femoris muscle with surgery [6, 7]. To our best knowledge, only one placebo-controlled, non-randomized trial has compared BoNT-A and placebo injection of the rectus femoris muscle to reduce stiff knee gait (SKG) [35]. The 100–125 U onabotulinumtoxinA group showed a significant reduction in spasticity with improved knee kinematics, energy expenditure during walking, and functional assessments after 2 months versus the placebo group [35] (Table 1).

In a prospective observational study on 22 stroke survivors with SKG, 150–200 U onabotulinumtoxinA into rectus femoris muscle under electrostimulation guidance reduced the MAS score of the knee joint. The spontaneous gait speed was significantly increased from baseline after BoNT-A and the percentage increase in peak knee flexion was correlated to percentage increase in peak knee flexion following a voluntarily increase in gait speed before BoNT-A injection [36] (Table 1).

Another trial in stroke subjects described the effects of rectus femoris treatment with onabotulinumtoxinA (mean dose 164 U ± 49 U) [37]. Dynamometer data showed that peak knee extensor torque was significantly decreased, and peak knee flexor torque was significantly increased during maximal voluntary concentric and isometric contractions after injection of the rectus femoris, whereas functional outcomes, such as 6MWT, 10MWT at maximal gait velocity, 10MWT at spontaneous gait velocity, TUG, time to ascend stairs, and time to descend stairs did not change [37]. Therefore, BoNT-A injections decreased the spasticity modifying knee extension and flexion torque, but without an impact on functional tests [37] (Table 1).

Overactivity of the rectus femoris is often a cause of SKG [38, 39], but altered activity of other muscles such as underactive iliopsoas or overactive triceps surae or vasti could contribute [40]. In this case, simultaneous BoNT-A injections into several spastic muscles could be appropriate, as shown by Caty and colleagues in 20 stroke patients with SKG treated with onabotulinumtoxinA injected into rectus femoris (200 U), semitendinosus (100 U) and triceps surae (200 U) muscles under EMG or electrical stimulation

guidance [41]. At 2 months, onabotulinumtoxinA reduced tone in rectus femoris, semitendinosus and triceps surae muscles. Gait analysis showed increased knee flexion during the swing phase, decreased external mechanical work, and lower energy cost, representing improved locomotion ability in the patients [41] (Table 1).

Some patients with stroke have severe hip and knee flexion and this picture hampers gait, posture, and both active and passive movements. The flexor pattern is caused by muscle hypertonia and contractures of the iliopsoas, rectus femoris, tensor fasciae latae, adductors, internal hamstrings, and biceps femoris. The use of BoNT-A to reduce hyperactivity of hip and knee flexor muscles was described in an open-label observational study in 9 stroke patients [42]. Subjects received 300–400 U onabotulinumtoxinA to the iliacus region of the iliopsoas and knee flexors and, when necessary, to other muscles of the hip and knee under electrical stimulation guidance. Evaluation at Weeks 10 ± 2 and 21 ± 3 after treatment showed modest reductions in MAS score with little increase of passive hip extension. Greater benefits were found on passive functioning, including toileting, dressing and transfers, as well as pain reduction at rest and during mobilization. No changes in active function were observed [42] (Table 1).

In stroke patients, it is not uncommon to observe fixed or discontinuous flexion of hallux and fingers or extension of hallux due to overactivity of flexor hallucis (longus and brevis), flexor digitorum (longus and brevis), extensor hallucis longus, and extensor digitorum longus.

These conditions are painful and disabling, causing abnormal posturing of the foot and difficulty in wearing shoes. They are usually secondary dystonias, especially persistent extension of the great toe, and not patterns of spasticity. Yelnik and colleagues described the efficacy of onabotulinumtoxinA treatment under electrical stimulation guidance in 11 stroke subjects with overactivity of the extensor hallucis longus muscle. Eight patients received the injection only to extensor hallucis longus (66–100 U), three subjects also to tibialis anterior and posterior muscles [43]. After 16 injections over 4 months, extensor hallucis longus overactivity disappeared in 10 patients and subjective assessment was very good for reduced pain and shoe wearing difficulties and was good or very good at 3 months for 8 patients who received 12 injections [43] (Table 1). Finally, in a single-center, open-label, prospective study in 14 stroke survivors with spastic toes, onabotulinumtoxinA was injected at 25–35 U per muscle with AS = 2, from 50–70 units per muscle with AS = 3, and from 75–95 units per muscle for AS = 4 [44]. There were improvements in all outcome measures (MAS, a visual pain scale, and a self-rated visual scale on percentage of function) lasting from 5/6 months to 2 years, without adverse effects [44] (Table 1).

5 High Doses of Botulinum Toxin Type A for Post-stroke Lower Limb Spasticity

Current guidelines suggest the use of up to 600 U of onabotulinumtoxinA and incobotulinumtoxinA or up to 1500 U of abobotulinumtoxinA per injection session to treat spasticity after stroke [2]. However, in recent years higher total session doses have been reported, which implies the treatment of a larger number of muscles and, therefore, use of the same dose into each muscle, in accordance with previous studies [45, 46].

Few reports described the employment of higher doses for lower limb spasticity in stroke survivors [47–50] (Table 2). Baricich and colleagues evaluated the efficacy and safety of higher doses of onabotulinumtoxinA (from 600 to 800 U) injected in 26 stroke subjects with upper and/or lower limb spasticity [47]. The mean total dose for thigh muscles (rectus femoris, biceps femoris, adductor longus/brevis/magnus) was 75.6 ± 21.3 U, whereas for lower leg muscles (medial gastrocnemius, lateral gastrocnemius, soleus, flexor hallucis longus, flexor digitorum longus, tibialis posterior, tibialis anterior, extensor hallucis longus) it was 404.4 ± 112.4 U. A significant muscle tone reduction was observed 30 days and 90 days after injection for thigh and leg muscles with functional improvement and no adverse events [47] (Table 2). Hesse and colleagues reported use of high doses of BoNT-A in 6 patients affected by lower limb spasticity after stroke, injecting 1500–2000 U abobotulinumtoxinA into medial gastrocnemius, soleus and tibialis posterior muscles under EMG guidance and employing electrical stimulation after treatment [48]. One subject treated with 2000 U abobotulinumtoxinA developed bladder paresis, requiring catheterization for 14 days. All the patients reported muscle tone reduction, whereas only recipients of electrical stimulation improved gait velocity, stride length, stance and swing-symmetry at 4 weeks of follow-up [48] (Table 2).

Several studies of high doses of incobotulinumtoxinA investigated the possible reduced formation of BoNT-A antibodies due to the absence of complexing proteins, even though the European product label recommends a maximum dose of 400 U for upper limb post-stroke spasticity. A prospective, nonrandomized, open-label study evaluated higher doses of incobotulinumtoxinA administered under ultrasound guidance in 25 consecutive subjects with upper and lower limb post-stroke spasticity [49]. Doses ranging from 250 to 340 U were injected into the lower limbs distributed in the ankle plantar flexors (medial gastrocnemius, lateral gastrocnemius lateralis, and soleus) (140–230 U), adductor longus–brevis–magnus (50–80 U), rectus femoris (50 or 60 U), biceps femoris (50 U), tibialis posterior (30–50 U), tibialis anterior (30 U), flexor digitorum longus (30 or 40 U), flexor hallucis longus (20–40 U), and extensor hallucis longus (30 or 40 U). Thirty and 90 days after the treatment,

patients showed significant reductions in disability, spasticity-related pain, and muscle tone measured with disability assessment scale, the visual analogue scale, and AS. Only 16% of patients experienced treatment-emergent adverse events (injection site pain and muscular weakness) [49] (Table 2). In a follow-up study on the same sample, after two years of BoNT-A administrations (8 sets), the remaining 20 of 25 subjects, treated with higher doses (260–460 U) to lower limbs continued to report spasticity and disability reductions as measured 30 days after the last set of injections compared to baseline, without severe adverse effects [50] (Table 2).

Therefore, current evidence suggests that higher doses of BoNT-A are effective in reducing spasticity of the lower limbs after stroke, with only rare occurrences of mild adverse effects [46]. However, even if systemic BoNT-A toxicity is a rare event, this is still the most vigorous concern regarding use of higher doses. In fact, after administration, BoNT-A remains mainly localized at the injection site, and this probably accounts for its generally acceptable safety profile [51]. However, spread to contiguous areas is likely to increase the risk of adverse effects and, even if uncommon, distant spread can also occur causing unintended neuromuscular blockade away from the injection site with symptoms such as generalized weakness [52] and flu-like syndrome [53]. With regard to this issue, no clear differences have been reported between the various BoNT-A preparations [19]. In addition, several factors other than the pharmaceutical preparation could affect the local and remote spread of BoNT-A, such as dose, dilution, injection technique, target site, location of injection within the muscle belly, depth of injection, level of muscle hyperactivity, and post-injection rehabilitation treatment [47, 54, 55]. In assessing the possible benefits of higher doses, it must be considered that, despite the observed reduction of muscle tone, there is limited evidence that higher doses in the lower limbs are related to a significant functional improvement, although this might be related to several other possibilities. Indeed, it is recognized that in severe spasticity, meaningful improvement in active performance may be difficult to obtain even with BoNT-A treatment [46]. Conversely, high doses may be appropriate in several neurological conditions to reduce muscle tone and improve hygiene, gait, and balance [56]. It should also be considered that any impact on well-being and life satisfaction may only be detectable with patient-reported outcome measures, rather than quantitative measures [57–59]. Additionally, it should be remembered that post-stroke spasticity has an afferent, sensory component, which may lead to differences in the sensations described by patients [59]. Finally, another critical issue is the possible impact of higher doses on inter-injection intervals [46]. If this can be demonstrated, a reduction in the number of treatments needed could have a beneficial impact on health and social costs.

6 Botulinum Toxin Type A as Early Treatment for the Post-stroke Spasticity of Lower Limb Muscles

Recent RCTs have stimulated increased interest in the employment of BoNT-A in the subacute (early) phase, to reduce disabling muscle contracture and stiffness in the paretic upper [60] and lower limbs [61, 62] (Table 1). Such early use has been proposed [60–62], even if, at present, doubts exist about the definition of 'early' treatment and the reasons for it. A single-center double-blind RCT was performed to investigate the efficacy of BoNT-A in reducing muscle hypertonicity at the ankle within the first 3 months after stroke [61]. Thirty-five stroke survivors with spastic pes equinovarus were allocated to receive either 230 U onabotulinumtoxinA or placebo; a second open-label injection was optional at Week 12. Subjects who received onabotulinumtoxinA significantly improved (mean MAS score) over the first 12 weeks, while placebo recipients showed no significant change; there was also a significant difference in spastic muscle tone between the two groups. Moreover, onabotulinumtoxinA treatment at study start produced comparatively lower MAS scores at all time points to Week 24 compared to treatment with placebo and then onabotulinumtoxinA. These findings suggested that early BoNT-A treatment could further reduce the risk of increased muscle tone after stroke [61] (Table 1).

The efficacy of BoNT-A in lower limb spasticity in subacute stroke patients was also assessed in a Phase II RCT in which low-dose BoNT-A improved spasticity, gait, and daily living abilities in 23 individuals treated within 6 weeks of stroke [62]. Participants were randomly allocated to 200 U onabotulinumtoxinA (150 U to triceps surae and 50 U to tibialis posterior) or placebo, under electrical stimulation guidance. Lower limb MAS scores, gait analysis (step length, cadence, speed), 6MWT, Fugl-Meyer Assessment (FMA) and modified Barthel index (MBI) assessment were performed before and at 4 and 8 weeks after treatment. At Week 8, MAS scores in the BoNT-A group were lower than those in the control group. FMA, MBI, step length, cadence, speed, and 6MWT distance were also better in the treatment group than in the control group [62] (Table 1).

7 Botulinum Toxin Type A Compared with Other Therapies for Post-stroke Spasticity of Lower Limb Muscles

Few studies have compared BoNT-A with other treatments for post-stroke lower limb spasticity [63–66] (Table 3). Kirazli and colleagues compared EMG-guided 100 U onabotulinumtoxinA with 3 mL of 5% phenol neurolytic injected to medial and lateral gastrocnemius, soleus, and tibialis

posterior muscles [63]. Patients in both groups showed reductions in AS score from baseline at follow-up, which were significant only for the BoNT-A group. Comparing the two groups, AS scores were significantly better for the BoNT-A group at Weeks 2 and 4, but at Weeks 8 and 12 there were no statistically significant differences, suggesting BoNT-A to be more effective only in the short term [63] (Table 3).

Rousseaux and colleagues compared the effects of BoNT-A and tibial nerve neurotomy in an open-label study of 34 patients with spastic foot after stroke, with 300 U onabotulinumtoxinA injected under electrical stimulation guidance into soleus, medial and lateral gastrocnemius, tibialis posterior and tibialis anterior, flexor digitorum longus and flexor hallucis longus—depending on the main distal spasticity pattern [64]. Neurotomy was performed with a 6- to 12-month delay on the motor branches of the tibial nerve. Subjects were assessed using MAS, passive and active ROM for ankle movement, balance and functional ambulation categories, gait velocity, step length and Rivermead motor assessment. In this RCT, tibial nerve neurotomy appeared to be more effective than BoNT-A therapy on most of the functional parameters [64] (Table 3). Selective tibial neurotomy versus BoNT-A therapy has also been compared in another RCT in 16 chronic stroke patients presenting equinovarus spastic foot; 8 underwent tibial neurotomy and 8 received onabotulinumtoxinA injections. The soleus (200 UI) was injected in all 8 patients, and tibialis posterior (125 UI) and flexor hallucis longus (75 UI) were treated in 4 patients. Outcome measures were spasticity on the Tardieu Scale, the MAS score of triceps surae, tibialis anterior strength on the Medical Research Council scale, passive ROM of the ankle, spontaneous walking speed (with usual walking aids) on the 10MWT. Participants were assessed before intervention and at 2 and 6 months after treatment. Compared with BoNT-A, tibial neurotomy produced a greater reduction in ankle stiffness. Both treatments induced comparable improvements in ankle kinematics during gait, whereas neither induced muscle weakening [65] (Table 3).

Finally, Picelli and colleagues compared the effects of therapeutic ultrasound and transcutaneous electrical nerve stimulation (TENS) with BoNT-A on spastic pes equinus after stroke [66]. Thirty patients were randomly assigned to three groups: one group received therapeutic ultrasound to the affected leg calf muscles, one group underwent TENS to the tibial nerve of the affected leg, and one group was injected with 200 U onabotulinumtoxinA to the spastic gastrocnemius under ultrasound guidance (100 U for medial gastrocnemius and 100 U for lateral gastrocnemius). All subjects were evaluated immediately before treatment and 15, 30 and 90 days after the first clinical evaluation for passive ankle dorsiflexion ROM and the MAS. Those treated with onabotulinumtoxinA had significantly better passive ankle ROM than those treated with physical modalities at all post-treatment evaluations [66] (Table 3).

8 Discussion

The cumulative body of evidence from the studies reviewed in this article suggests that BoNT-A appears to be safe and efficacious in reducing lower limb spasticity after stroke. Indeed, several studies and meta-analyses indicate that BoNT-A injections are the treatment of first choice for focal spasticity [15]. Although controversy exists about improvements in motor function relative to spasticity reduction after BoNT-A treatment, an improvement of sensorimotor function (FMA) has been demonstrated in a systematic review and meta-analysis, but without gait speed gains [67]. In fact, this pooled analysis suggested more persistent clinical benefits in lower limb spasticity and FMA score than placebo in patients after stroke even if the small number of analyzed RCTs did not permit a robust conclusion, considering the extreme variability of protocols, doses, injected muscles, and clinical features of patients (spasticity, weakness, contractures, tendon retractions) [67]. Other recent meta-analyses and systematic reviews have not supported an effect of BoNT-A treatment on quality of life measures, active outcomes, or gait for the lower limb [68, 69].

Another interesting aspect of BoNT-A therapy for lower limb spasticity regards the doses to be injected. The licensed indications and doses are different for the various marketed formulations. In the USA, the maximum abobotulinumtoxinA dose approved for stroke survivors is 1000 U, and only for upper limb spasticity, whereas the approved maximum dose of onabotulinumtoxinA is 400 U for upper limb spasticity and 300–400 U for ankle plantar-flexor spasticity. IncobotulinumtoxinA is approved at a maximum 400 U dose for subjects affected by upper limb spasticity, without any indication for lower limb [15, 17]. In Italy, onabotulinumtoxinA and abobotulinumtoxinA are licensed for equinus foot due to triceps surae spasticity at the maximum doses of 400 U and 1500 U, respectively, whereas incobotulinumtoxinA is not approved for lower limb spasticity. The majority of stroke survivors with lower limb spasticity are usually treated with BoNT-A doses ranged from 50 U to 100 U (incobotulinumtoxinA and onabotulinumtoxinA) and 150 U to 300 U (abobotulinumtoxinA) administered into ankle plantar-flexors muscles, even if several lower limb muscles are injected, depending upon the clinician's experience and patient's clinical picture. The initial and subsequent dosages should be adjusted based on the size, number and location of muscles involved, spasticity severity, the presence of local muscle weakness, and the patient history of response to, and adverse events with, previous botulinum toxin treatment.

Recently, clinicians have considered the possibility of reducing SKG and hamstring contractions with BoNT-A [42, 70]. Several studies have shown the functional effects of this treatment, especially on kinematic parameters [71], and BoNT-A administration to rectus femoris can achieve a gain of 5–8 degrees in peak knee flexion during the swing phase of gait [35, 41, 70, 72]. However, it was considered that the percentage improvement in peak knee flexion in the fast gait condition before injection was the only parameter correlated with the percentage increase in peak knee flexion after rectus femoris muscle BoNT-A treatment [36].

Despite the large number of studies conducted on the use of BoNT-A for lower limb spasticity, the results of outcome measures and spatio-temporal parameters changes following BoNT-A are often small and are affected by many variables [73]. Sometimes the treated subjects reported subjective improvement during gait even if the clinicians did not observe any changes in mobility measures. This could be explained by a BoNT-A effect on the heaviness and unpleasant sensation that can reduce the quality of life of stroke survivors with upper and lower limb spasticity [74].

During the evaluation of subjects with chronic stroke, it is appropriate to consider using BoNT-A to treat the intrinsic and extrinsic foot muscles responsible of equinovarus posture and great toe painful spasms during gait or while wearing shoes. Targeting the right site for BoNT-A injections is important to optimize the effect. To date, there are no recommendations about which techniques are most suitable; however, ultrasound guidance permits in real time the evaluation of position and muscle characteristics, such as fat and fibrosis areas, which should be avoided. This issue is key, as confirmed by several studies using ultrasound technique [34, 75]. In another study comparing injection techniques, the medial gastrocnemius muscle of 81 subjects with spastic equinus was significantly thicker than the lateralis on ultrasound evaluation, so the overall accuracy of needle injection was significantly higher for the medial gastrocnemius than for the lateral (92.0% vs 79.0%). In contrast, neither manual needle placement nor electrical stimulation guidance showed complete accuracy, when measured using ultrasonography [75].

9 Conclusions

In stroke survivors, BoNT-A therapy has shown efficacy for spasticity reduction and safety in the lower limb, particularly at higher doses. Controversies still exist, however, for gait improvement. Further well-designed, large RCTs are required to show whether such objective gait measures can be confirmed in patients with documented reduction in spasticity following BoNT injection. Finally, specialized training in patient assessment, BoNT-A dosage, injection technique, and side-effect knowledge are essential to maximize the possibility of benefit for patients receiving this treatment for spasticity after stroke.

Compliance with Ethical Standards

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Conflicts of interest Andrea Santamato, Nicoletta Cinone, Francesco Panza, Sara Letizia, Luigi Santoro, Madia Lozupone, Antonio Daniele, Alessandro Picelli, Alessio Baricich, Domenico Intiso, and Maurizio Ranieri have no conflicts of interest that are directly relevant to the content of this study.

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