BREAKING A DOGMA:
HIGH DOSES OF INCOBOTULINUMTOXIN A ALLOW TO TREAT SEVERE LIMB SPASTICITY IN THE COMPLEXITY OF THE CLINICAL PATTERNS
A RETROSPECTIVE MULTICENTRE STUDY

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INTRODUCTION

Botulinum toxin type A (BoNT-A) is the treatment of choice in patients with severe spasticity. The use of dosing schedules is controversial; therefore, the management of treatment is often operator-dependent. Recently, the TOWER study[1] demonstrated the safety and efficacy of incobotulinumtoxinA (Merz Pharmaceuticals, Frankfurt, Germany) doses up to 800 Units. The aim of this study was to ascertain whether there is any evidence of recurring dosage schemes and in what relationship they are with the current recommendations (**tab.1**).

Table 1. Dosing guidelines for adult and children as suggested by the consensus opinion of the Spasticity Study Group.

	Adults	Children
Total maximum body dose per visit	400 – 600 Units	Lesser of 16 Units per kg or 400 Units
Reinjection	≥ 3 months	≥ 3 months

Note: the suggested doses in this table represent updates to the original dosing recommendations (see Mayer NH, Simpson DM, editors. *Spasticity: Etiology, Evolution, Management, and the Role of Botulinum Toxin Type A*. New York WE MOVE, 2002).

METHODS

This is a retrospective study concerning BoNT-A therapy administration over the past three years in 4 centers of the south of Italy. We collected data on patients with severe upper and/or lower limb spasticity due to encephalic or medullary lesions and regularly receiving incobotulinumtoxinA at intervals of about three months.

RESULTS

We enrolled 74 subjects from 4 different centres, 69 adult (30 females) and 5 pediatric (1 female) patients. Overall, they had a mean age of 50±18 years ranging from 3 to 85. A total of 364 injections were analysed meaning an average of about 5 sessions per patient. **Table 2** includes information on scheduling and dosing in adult and younger patients stratified by region of injection (total body = TB, upper limb = UL and lower limb = LB). To note, at least 5% of adults were treated using a TB dosage greater than 600U.

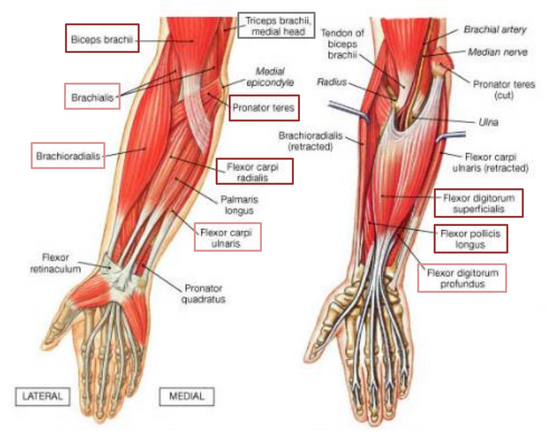
Table 2. Overview of management of upper and/or lower limb spasticity using incobotulinumtoxinA in adult and pediatric patients in clinical practice.

	Adults (N=69)		Children (N=5)	
Scheduling				
Total N injections	TB=342; UL=261; LL=217		TB=22; UL=17; LL=22	
N sessions/patients mean (min-max)	5 (1 to 12)		4 (2 to 8)	
Interval between injections (weeks); median; [25° - 75°]	20 [16 to 32]		24 [18 to 28]	
Dosing (Units/visit) *mean±SD; (min – max)*	Unilateral	Bilateral	Unilateral	Bilateral
Total body	332±133 (80 to 830)	955±304 (400 to 1600)	156±93 (65 to 290)	424±104 (320 to 600)
Upper limb	284±113 (65 to 780)	333±111 (200 to 500)	25±11 (15 to 40)	---
Lower limb	175±108 (50 to 550)	459±112 (200 to 600)	130±88 (50 to 260)	212±52 (160 to 300)

LL = lower limb; SD = standard deviation; TB = total body; UL = upper limb.

Regarding the number of sites that were simultaneously treated in the same patient and during the same visit, we observed the following patterns (mean (min-max)): adults UL: 4 (1 to 7); LL: 2 (1 to 5); pediatric UL: 1 (1 to 1); LL: 2 (1 to 4).
In UL, the treatment was mainly focused in muscles of forearm and in particular, in muscles that move wrist, hand and digits (**fig.1A**); triceps brachii was injected in less than 10%. Muscles that move the pectoral girdle were only partially involved, about 15-25% of total injections (trapezius and major pectoralis, respectively).
On the other hand, the major clinical patterns in LL simultaneously involved several groups of muscles from the higher to the lower leg and foot/toes (**fig.1B**).

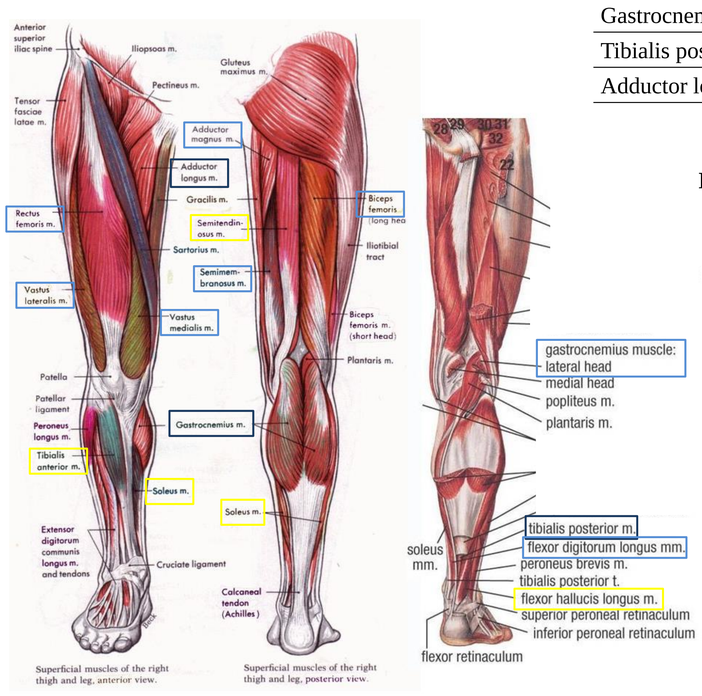
A



	Units/muscle mean; [min – max]
Biceps brachi	87 [50 to 200]
Pronator teres	63 [25 to 100]
Flexor digitorum prof.	72 [40 to 200]
Flexor digitorum sup.	71 [20 to 200]
Flexor carpi radialis	70 [40 to 200]

Mean value of percentage of injections
40-60%
20-30%
<10%

B



	Units/muscle mean; [min – max]
Gastrocnemius	65 [25 to 200]
Tibialis posterior	65 [30 to 130]
Adductor longus	122 [50 to 200]

Mean value of percentage of injections
30-50%
10-20%
5-10%

Figure 1. Most treated muscles in adults affected by sever spasticity and related mean dosage of incobotulinumtoxinA (Units/muscle) in upper (**A**) and in lower limb (**B**). Dosing are reported for muscles with greater than 30% of total injections.

CONCLUSION

Our findings show that incobotulinumtoxinA is regularly used at high dosage schemes both at a focal and above all at a global level reflecting the complexity of the clinical patterns; indeed, the safety and efficacy of this innovative approach allows patients with severe limb spasticity to be treated in a number of muscle sites greater than routinely recommended under the same visit. Noteworthy, this picture from a retrospective collaborative registry seems to support a benefit of incobotulinumtoxinA for the treatment of LL spasticity in spite of FDA-approved indications that suggest its use to treat UL spasticity only (revised Food and Drug Administration approval 12/2015).

REFERENCES

1.Wissel J, Ferreira JJ, Molteni F, Satkunam L, Moraleda S, Rekand T, McGuire J et al. Safety and efficacy of incobotulinumtoxinA doses up to 800 U in limb spasticity. Neurology 2017;88(14):1321-1328.