Indirect Treatment Comparison of Botulinum Toxins A for the Treatment of Pediatric Upper Limb Spasticity

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BACKGROUND

- Botulinum neurotoxin type A (BoNT-A) is used in the management of upper limb spasticity (ULS) in children.
- BoNT-A, in combination with occupational therapies, aims to improve limb function and allow for active participation, and to prevent or delay future musculoskeletal complications.

OBJECTIVE

- The objective of this analysis, considering the lack of head-to-head studies, was to evaluate the relative efficacy and safety of BoNT-A products across diverse published studies, when used to manage spasticity in children

METHODS

Patients

- Children (aged <18 years) experiencing ULS symptoms.

Design and treatment

- Systematic search and identification of published randomized controlled trials (RCTs).
- Any dose of abobotulinumtoxinA (aboBoNT-A; Dysport®) or onabotulinumtoxinA (onaBoNT-A; Botox®) or placebo.
- If a study did not have a placebo or a 'no treatment' arm, the lowest dose or least intensive intervention was analyzed as no treatment.

Study endpoints and assessments

- Change from baseline (CFB) in Modified Ashworth Scale (MAS) or Ashworth Scale (AS) scores at weeks 6 and 16.
- Responder rates (percentage of patients with at least 1-unit change.
  - Derived assuming that MAS/AS CFB followed a normal distribution with mean of 1 unit. A corresponding standard deviation (SD) was assumed equal to the average of SDs reported in individual studies.
- Safety (serious adverse events).

Data analyses

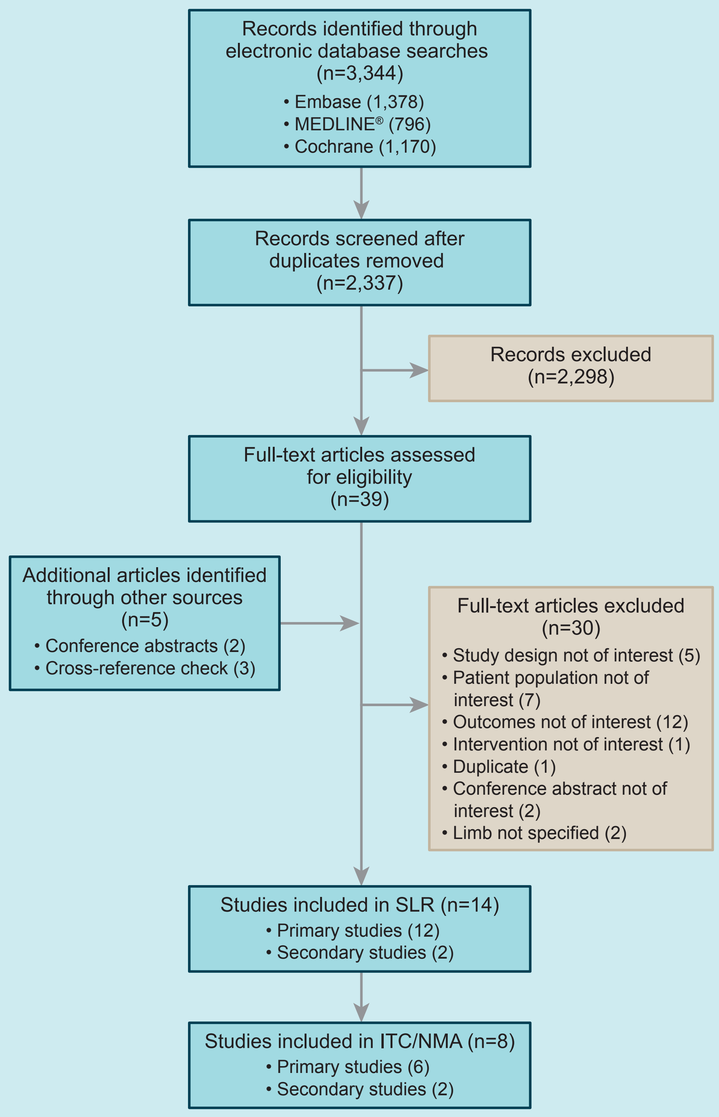
- A systematic literature review was conducted in March/April 2019, searching MEDLINE® from 1946 to 2019; EMBASE® (Ovid SP®) from 1974 to 2019; and the Cochrane Central Register of Controlled Trials (OVID SP®) in March 2019.
- Supplementary searches identified studies from grey literature, ClinicalTrials.gov and relevant conference material during 2017 to 2019.
- Study quality assessment used the adapted Cochrane risk of bias 2.0 tool for randomized trials.
- MAS/AS response rates were analyzed through Bayesian network meta-analysis (NMA). A probabilistic approach was deemed appropriate, allowing for a whole distribution of values for the normal approximation of response.
- Indirect treatment comparisons (ITCs) were carried out for other outcomes through the Bucher method.
- For the Bucher ITC, statistical heterogeneity between the studies on each direct treatment comparison was assessed through the I^2 statistic and the p-value of the Q-statistic.

RESULTS

Evidence base and NMA feasibility assessment

- Out of 2,337 articles identified from the searches, 14 articles reported findings of children with ULS (**Key Figure**).
  - Three studies did not have a 'no treatment' or low-dose aboBoNT-A arms to form links to other treatments within the network, and in three studies, the dosages used were not licensed. Two articles were secondary publications of a previously published study.

Key Figure. PRISMA diagram



ITC, indirect treatment comparison; NMA, network meta-analysis; SLR, systematic literature review.

- Six original RCTs were included in the ITC/NMA.[1–6]
- One study included aboBoNT-A treatment arms[2] and five studies included onaBoNT-A treatment arms.[1,3–6]
- Sample sizes ranged from 11 to 123.
- All analyses were based on a network of four interventions: aboBoNT-A 8 U, aboBoNT-A 16 U, onaBoNT-A (doses pooled within the approved range, up to 8 U/kg and 400 U in total) and placebo/no treatment. One study (NCT0210635113) included an aboBoNT-A 2 U arm instead of 'no treatment', which was analyzed as equivalent to placebo and occupational therapy. This allowed for an evidence network with onaBoNT-A via the common comparator ('no intervention').
- Depending on the endpoint, the network was informed by 2–4 studies.
- A sensitivity analysis was conducted excluding a study introducing a large amount of heterogeneity due to differences in study design.[4] Exclusion of this study from the MAS/AS week 6 analysis, for instance, reduced I^2 from 89.2% to 0%.

NMA results

- In the base case, a relative risk for MAS/AS score CFB between the two treatments at weeks 6 and 16 showed a 95% confidence interval (CI) including 0, and no statistically significant difference in treatments could be found, with a consistent numerical trend in favor of aboBoNT-A.
- In the sensitivity analysis, aboBoNT-A was significantly more effective than onaBoNT-A for MAS/AS score CFB, across the time points.
- When transforming results into responders rates (% [95% CI]), we estimated that, at week 6, 73% (36%, 94%) of patients responded to treatment with aboBoNT-A 8 U/kg, 80% (44%, 97%) with aboBoNT-A 16 U/kg and 71% (47%, 87%) with onaBoNT-A (pooled doses), respectively (**Table 1**).
- At week 12, responder rates were estimated at 58% (28%, 84%) for aboBoNT-A 8 U/kg, 66% (35%, 89%) for aboBoNT-A 16 U/kg and 51% (31%, 70%) for onaBoNT-A (pooled doses), respectively.

Table 1. MAS/AS responder rates – Bayesian NMA (random effects models)

A) Week 6

Intervention	Median % of responders	95% CrI
No treatment	54	41.6; 66.7
OnaBoNT-A	71	46.5; 87.4
AboBoNT-A 8 U/kg	73	36.0; 94.4
AboBoNT-A 16 U/kg	80	44.4; 96.5

B) Week 12

Intervention	Mean % of responders	95% CrI
No treatment	42	30.9; 54.4
OnaBoNT-A	51	31.4; 70.0
AboBoNT-A 8 U/kg	58	28.0; 84.2
AboBoNT-A 16 U/kg	66	35.4; 89.0

AS, Ashworth Scale; CrI, credible interval; MAS, Modified Ashworth Scale.

- The relative risk comparing serious adverse events for aboBoNT-A with onaBoNT-A was 0.33 (95% CI 0.02, 5.36) for both aboBoNT-A dosages. The point estimate indicates that patients in the aboBoNT-A arm were less likely to have an adverse event of any type; however, the difference in risk was not statistically significant. Safety endpoints were not significantly impacted for aboBoNT-A in comparison with onaBoNT-A in the sensitivity analysis.
- These results need to be interpreted in the context of the key differences in study designs:
  - The aboBoNT-A trial[2] included a low-dose injection (2 U/kg), termed 'no intervention', which could have resulted in an underestimation of relative effects (difference in CFB and relative risk) comparing aboBoNT-A with onaBoNT-A via a common comparator ('no intervention'), resulting in an biased comparison in favor of onaBoNT-A.
  - Only one trial of onaBoNT-A was double-blinded,[7] while the other studies included were either single-blinded[3] or open-label.[4,5,8] In contrast, the aboBoNT-A trial was double-blinded,[2] had a high-quality design and was statistically robust.
  - The aboBoNT-A trial included an assessment point at 16 weeks, which was 4 weeks longer than the observed time horizon in most trials of onaBoNT-A. Pooling these data could favor onaBoNT-A, since the 16-week assessment point in the aboBoNT-A trial is further beyond the waning of the treatment effect (which starts from week 8).[9] In the week 16 analyses, aboBoNT-A demonstrated favorable point estimates compared with onaBoNT-A, which may be indicative of its longer duration of effect, described previously.[10]

CONCLUSIONS

- For the treatment of spasticity in the upper limbs of children, there was a favorable trend for aboBoNT-A on point estimates of efficacy and safety, which became significant when sensitivity analyses were performed to exclude studies inducing a large amount of heterogeneity. The results could be conservative in the context of the mentioned differences in study designs.
- The availability of just one double-blind onaBoNT-A study, small sample sizes and, importantly, differences in study design hinder definitive conclusions. IncobotulinumtoxinA (Xeomin®) is not included in this analysis, but has now been approved by the FDA.
- More confirmatory evidence is needed in this area, as well as more research into the economic and quality-of-life impact of these interventions.

References

1. Fehlings D et al. Dev Med Child Neurol 2018;60(S3):33; 2. Delgado M et al. Dev Med Child Neurol 2020; doi: 10.1111/dmcn.1473 (Epub ahead of print); 3. Fehlings D et al. J Pediatr 2000;137(3):331–7; 4. Lowe K et al. Dev Med Child Neurol 2006;48(3):170–5; 5. Olesch CA et al. Dev Med Child Neurol 2010;52(1):79–86; 6. Rameckers EA et al. Neurorehabil Neural Repair 2009;23(3):218–25; 7. Fehlings D et al. Toxicon 2018;156(S33); 8. Speth LA et al. Dev Med Child Neurol 2005;47(7):468–73; 9. Nigam PK & Nigam A. Indian J Dermatol 2010;55(1):8–14; 10. Marque P et al. Ann Phys Rehabil Med 2017;60(Suppl):e24–5.

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