Reviewer's report

Title: Evaluation of the effects of Botulinum toxin A injections when used to improve ease of care and comfort in children with marked cerebral palsy: A double blind randomized controlled trial.

Version: 1 Date: 17 March 2012

Reviewer: Richard Placzek

Reviewer's report:

In general:
1. The paper describes a study design to evaluate the effect of Botulinum toxin injections in children with infantile cerebral palsy of high severity (GMFCS IV and V). Reliable data and more knowledge about this particular therapeutic area are desirable.

Major Compulsory Revisions

About Background:
2. Page 3: “When injected into target muscle, BoNT-A enters the presynaptic terminal, and binds to acetylcholine preventing its release and thus reducing spasticity.” is not correct. BoNT-A does not bind directly to acetylcholine but to one, in vesicles located receptor. After cleavage of the active portion of the BoNT leaves of these vesicles and inactivates SNAP 25, which leads to a prevention of the exocytosis of acetylcholine.
The basics must be represented correctly.

3. Method / Design:
In children between 2 and 16 years the relationship between spasticity and contracture of the muscles are very heterogeneous.

Page 3 "Spasticity commonly leads to muscle contractures ...". For very young children are more likely to outweigh the spastic component, with the older children more likely outweighs the structural component.

The study group should be divided into age groups (eg 2-6, 6-10 and 10-16 years). Alternatively, it could also be a subdivision according to the weighting of spasticity (dynamic movement restriction) and contracture of muscles (structural restriction of movement). The relationship between pain and the relationship between contracture / spasticity is not known. The described “Assessment of spasticity and range of motion” (page 15) will hardly be sufficient.

4. Only two follow-up examinations after 4 weeks and 4 months seem inadequate. After 4 weeks the drug effect of the BoNT-A is safe there. Whether this is still present after 4 months, in an individual case is unclear.
We recommend that two additional follow-up that is after 8 weeks and 6 months (if not more BoNT effect is present). The proposed phase 2 could be connected directly, so that would last for the duration of the study 12 months.

5. Study treatment:
The planned maximum dose of 12 U / kg / body weight (or 400 units maximum), we consider a good choice.

Other recommended maximum doses, such as the "European consensus table 2006 on Botulinum toxin for children with cerebral palsy" and "The updated European Consensus 2009 on the use of Botulinum toxin for children with cerebral palsy" by Heinen et al. however, should be mentioned and discussed.

Minor Essential Revisions

6. Title page:
The authors are provided with the numbers 1 and 2. The number 3 (Queensland Children's Medical Research Institute, ...) cannot be find.

7. From a scientific point of view a sham injection seems to be much more complicated, particularly with regard to blinding, than a real placebo treatment. From an ethical point of view it seems a workable compromise.

8. Reference List:
From 70 references, the latest are from the year 2010 (4x). The list should be updated and current publications will be added.

9. The reference number 24 (Delgado MR, et al.) is presented without a date (Neurology ??). The year should be added.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
The scientific work of the reviewer was supportet by the companies Allergan, Ipsen and Merz in the last five years.