Author's response to reviews

Title: Botulinum neurotoxin type A in the treatment of classical trigeminal neuralgia (BoTN): study protocol for a randomized controlled trial.

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Author's response to reviews: see over
Dear Ms Zakrzewska, dear Editor team,

First of all thank you very much for your valuable and helpful review of our study protocol. Before I address to your revisions, I would like to state that multiple changes in our publication have been made as you will find them in the revised, uploaded version of our protocol. But since this is a placebo controlled trial, strict legal regulations apply to it and major changes in the study protocol cannot be made without the consent of the ethical commission and the surveilling authorities. Patients have already been recruited and in this revision we can mainly focus on explain why we chose this specific study design.

Thank you for your comprehension. Please find below our point-by-point answer to the revision of the protocol and further of the required editorial changes. All changes in the manuscript are marked.

Best regards,

Jan Burmeister

Introduction

1 Minor: Although it is stated that BT-A has been shown to be effective it is not clear for how long this effect is present and whether it meant that other drug therapies were discontinued. Wu et al provide further details of the trial in response to a letter to the editor.

The related paragraph referring to the study by Wu et al. has been changed with regard to the details given in his response to the letter to the editor.

A response rate of 68%, defined as >50% VAS score reduction (as compared to 15% in the placebo group) has been reported after 12 weeks. Further details regarding the injection scheme, treatment allocation and the blinding procedure were not provided.

2. Major: The aim of the study should be clearly stated including whether this is a short or long term effect.

We expect the therapeutic effect of BT-A injects to be a short term effect, so that regular BT-A injections would be necessary. We believe that the analgesic effect of BT-A on TN is consistent with its effects on the neuromuscular junction. Open label follow up studies have suggested potential long term effects of BT-A in TN patients, but this has not yet been demonstrated in a double blind controlled trial (1). Since the patient collective entering our study is recruited from a tertiary care center patients are expected to have a chronic, overall therapy refractory course of disease. This is also why we expect a more moderate effect of BT-A. We have stated this more clearly in the introduction:
Subcutaneous injections of botulinum toxin type A are a promising treatment option for patients with unsatisfactory response to drug therapy or neurosurgical intervention. Its effects are expected to last for 3 months, so regular BT-A injections could be a potential short term treatment.

Methodology

3. Major: Given that the double blind phase starts at week 13 do the investigators estimate that the treatment effect will have worn off so patients will have had a return of pain? What if the patients are still pain free at week 12 therefore they are a responder would they receive further BT-A even though pain free?

Potential carry over effects have also been our concern, but given the assumed short term effect of BT-A, they should be of minor significance. Patients who do not have an average pain frequency of 3 / day cannot enter the second, double blind phase of the study. If there is an unexpected, overwhelming majority of patients with a satisfactory treatment effect after week 12, this data from single blind intervention will be reported instead.

4. Minor Injection sites: very few of these in comparison to other studies , how are the upper branches of V3 covered? If patients have pain in all 3 divisions do they get all the injection points whereas if they have only one division pain do they get only injections for that site?

In accordance to our experience with BT-A injections in TN, an injection scheme with fewer injection sites seems to be more tolerable and safe. It could be a feasible interventional treatment option also in other pain clinics. We expect a considerable diffusion of BT-A molecules over the area of the affected trigeminal branch, which should also sufficiently cover the V3 branches. Patients with all 3 branches affected will receive a total of 45 U of BT-A at the three injections sites whereas patients with only one affected branche will receive 15 U of BT-A at one injection site.

5. Major: How many investigators will be performing the injections? What experience have they had?

There will be three investigators performing the injections. All of them have more than one year of work experience in our clinic for headache and facial pain. All of them have experience with BT-A injections in the treatment of chronic migraine and other conditions. This is added in the methods section:

   There will be three investigators performing the injections who are experienced in the treatment of headache and facial pain and trained in BT-A injections.

6. Minor: Primary outcome measure is number of pain attacks – why was this
chosen rather than intensity?

Both number of pain attacks and reduction in pain scores are valuable outcome parameters. To us number of pain attacks is a more convincing, easily demonstrable variable to a TN patient who decides whether or not he would undergo BT-A injections.

7. Minor: Secondary outcomes please define HIT-6 and ADS which have never been used in TN studies and CGI. Why use SF12 – a very difficult scale to evaluate and would need to compare to population norms although is used in neuropathic pain scales. SF-36 only been used in a couple of surgical TN studies and not reported well.

Our experience in clinical trials is mainly in the field of headache research where the HIT-6, SF-12 and ADS are well established scales to evaluate disease burden and treatment efficacy. They are also used in other trials as well as in our daily patient care in the headache clinic (2).

8. Major: Concomitant drug therapy – the protocol states that this will be kept steady but surely the reason for use of BT-A is to reduce need for systemic drugs? How will the investigators prove that it is not the medication that has started to work or that the patients are going into a natural remission?

In order to prove the effect of BoTN, concimitant therapy needs to remain consistent from week 4 prior to baseline, although a reduction of systemic therapy would be desirable. Natural remission our symptom fluctuation can unfortunately never be ruled out. Concomitant therapy needs to be permitted for ethical reasons and a higher patient’s acceptance/compliance.

9. Major: Inclusion: at least an average of 3 paroxysms a day and a responder is defined as frequency reduction of 30% so how would this work in practice if a patient has only 4 paroxysms a day? What about severity as most trials suggest at least NRS of 4.

The average frequency of paroxysms per day relates to the overall number of paroxysms in the given week. So an average frequency of exactly 4 paroxysms per day reflects a total of 28 paroxysms in that week and a frequency reduction of >30% would be achieved if there was a total of 19 paroxysms (2.71 per day). This seems to be practicable to us.

10. Major: Power calculation: the number needed for the trial is very small and it would be expected that more patients are needed in the open label phase to ensure enough are recruited even though a 20% drop out is anticipated. Would you recruit more if you cannot get enough for randomization? A recent drug trial for TN needed around 60 in open label to get 29.
Discussion: this could include some potential problems in recruiting, whether the injections will be available after the end of the trial.
The single blind phase is not exactly open label. Prior to inclusion patients will be informed that they will receive at least one injection of BT-A, but not when exactly. This way we expect lower dropout rates and a lower confounding effect due to treatment expectations.

So far, the reimbursement of BT-A treatment costs is an individual decision made by the patient’s health care provider. We will address to the patient’s health insurance to support the reimbursement, if a patient benefits from BT-A. We have TN patients who have received BT-A off label and whose treatment cost are being paid by the health care provider. A regular follow up is possible in our botulinum toxin clinic.

Editorial requests:

1) Please move the trial registration number and the date of registration to the end of your abstract.

   Registration number and the date of registration have been moved to the end of the abstract

2) Please include the names of all ethical bodies that approved your study in the various centres involved. If you do not wish to list them all in the Methods section, please include the list as an additional file and refer to this in the Methods section.

   Since this is a single site trial there was only one ethics committee and one surveilling authority involved. Please find the addresses attached as an additional file.

3) Please state clearly whether or not you have funding in the Acknowledgements section. If there is no funding, please state this.

   A statement as been added in the Acknowledgements section.

References:


2. Holle D1, Burmeister J, Scherag A, Ose C, Diener HC, Obermann M; PredCH Study Group. Study protocol of Prednisone in episodic Cluster Headache (PredCH): a randomized, double-blind, placebo-controlled parallel group trial to evaluate the efficacy and safety of oral prednisone as an add-on therapy in