Author's response to reviews

Title: Intravenous immunoglobulin in the treatment of primary trigeminal neuralgia refractory to carbamazepine: a study protocol (ISRCTN33042138)

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Point to point reply to reviewers comments:

We are thankful for the detailed analysis of our paper by Prof. Nurmikko and Prof Meier and for their suggestions for adaptations in the paper.

Reply to Prof. Nurmikko:

1. Ambiguous inclusion criteria: This is an important point. We have now further detailed the Diagnostic Criteria of the IASP (International Association for the Study of Pain) in the 'Background' section and have referred to it again in the 'Methods' part. Although we agree that an atypical form of trigeminal neuralgia (TN) may frequently lead to confusion in diagnosis, we do not wish to mould entrance criteria along lines of typical or atypical forms as delineated in the Liverpool criteria (1). However, we agree that non-dominant continuous pain may frequently be found in patients with TN (the dominant pain remains of short duration). This is not delineated in the IASP criteria, and we will, therefore, in deviation from these criteria include patients with non-dominant continuous pain. We have now included this point in the methods section.

We agree that our entrance criteria will result in the inclusion of patients with slightly differing pain characteristics. We find it reasonable to maintain this, as we have previously observed a beneficial IVIG effect in patients showing both "typical" and "atypical" symptoms (unreported data). It shall be interesting though, once the study has been completed to analyse results in retrospective regards to differing pain upon entrance.

2. History of remissions: As delineated by the reviewer, patients with intolerable side effects to carbamazepine may respond well to other drugs. In this study we do not require, yet will tolerate the pre-treatment of patients with other drugs. The success rates of treatment with other drugs in TN refractory to carbamazepine are poorly characterized. Lamotrigine, which was found to be effective in a randomised, controlled trial for short term treatment (14 days) (2), has not yet been characterized in terms of its long term efficacy.

We agree that patients with a short history of TN are more likely to go into a spontaneous remission than those with a longer history. A safety mechanism is implemented in this study, preventing patients with high probability of spontaneous remissions entering; this is in the form of an one-week observation period at study onset (see 'Methods' section). Using entrance criteria as defined in our paper, we will not be able to eliminate effects from a favourable natural history on the significance
level of our results. On the other hand, modification of these criteria with the effect of exclusion of patients with short disease duration may well complicate the interpretation of our results and make generalisation difficult.

3. Quantification of paroxysms: We have now defined attacks as 'bursts of painful sensations', or 'paroxysms', and have largely replaced the word 'attack' with 'paroxysm' which appears more precise in this context. Patients will be able to count the number of paroxysms, e.g. as noted in the cited study by Zakrzewska, et al. Single stabs shall not be counted.

4. Funding for future treatment with IVIG: The ethical obligation to guarantee continued treatment of patients who respond well to IVIG will be funded through health schemes and industry. This can only be clarified when the exact participation of centers is finalized. Differing national regulations with regard to financiation must be taken into account.

Reply to Prof. Maier:

1. Patients refractory to Gabapentine: This important point addresses the (probable increasing) practice of using Gabapentine as first line therapy in TN. To date there are no results from randomised, controlled trials available confirming the efficacy of Gabapentine in TN. Gabapentin has been found to be efficient in other neuropathic pain conditions: painful diabetic neuropathy and post herpetic neuralgia. Clearly patients are frequently treated with Gabapentine as a first line therapy and the question arises, if, upon insufficient response to this drug, they should be required to receive treatment with Carbamazepine before being considered for the proposed trial. The reviewer commends to accept treatment failure with Gabapentin and to not require treatment with carbamazepine, "for clinical reasons".

We agree that pre-treatment with carbamazepine should not be performed as part of this study. We would, though, uphold the necessity for patients to have a carbamazepine trial before entering the study. This is considered essential because carbamazepine is cheap and has been proven effective in Trigeminal Neuralgia. It's profile of adverse advents is well described, while the efficacy and adverse events profile of IVIG are not yet known.

As this appears an important point, we have now clarified this in the 'Methods' section. In further discussing this we have also considered the option of requiring gabapentin pre-treatment in addition to carbamazepine pre-treatment. However, it was decided against this as no randomised trial has yet been published on gabapentin in TN. In addition, the costs of treatment with high doses of gabapentin at the present time may well be above those of treatment with IVIG (3).

2. Intention to treat: Patients terminating because of high pain levels or unsatisfactory adverse event profile are acting in accordance with the set major outcome criteria. Patients terminating for other reasons (e.g. travel related or because of unexpected private obligations) must be included into an intention to treat analysis. As this appeared to be unclear from the text, we have reformulated this important point (subheading: 'Primary outcome variable'). We are in agreement that operative treatment after enrolment must be considered as treatment failure, even in such cases where a patient may not formally withdraw from the study, or where the pain diary does not show high pain levels in accordance with set criteria. This is now mentioned under above subheading.

References: