Reviewer's report

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

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Reviewer: Prof Turo J Nurmikko

Level of interest: not specified

Advice on publication: Other (see below)

The study is designed to evaluate the effect of IVIG on a specific neuropathic pain condition, trigeminal neuralgia. The rationale is based on the authors' previous open-label study on a heterogeneous patient population with pain, and the observation that those with trigeminal neuralgia seemed to exceptionally well on this treatment (4 patients out of 6 improved by more than 66%; Goebel et al, Pain Medicine, 202;3:119).

Because the mechanism of trigeminal neuralgia is not known, and how IVIG intercepts with the generation of nerve pain is not clear, there are obvious difficulties in formulating a hypothesis for this trial to be based on. However, it is known from experimental and clinical studies that TNF-alpha expression is increased in painful, as opposed to nonpainful neuropathies (Empl al, Neurology, 2001;56:1371), and that pain is common in inflammatory neuropathies such as Guillan Barre Syndrome and CIDP (and in which conditions pain improves along motor recovery). The pathophysiology of trigeminal neuralgia is not fully understood; there appears to be a significant increase in the ability of the trigeminal ganglion cells to discharge repeatedly. The primary cause in most cases appears to be vascular compression at the dorsal root entry zone but in some cases this leads to excessive firing in (possibly just a small cluster of) trigeminal ganglion cells remains unresolved. Vascular compression itself does not lead to trigeminal neuralgia as imaging studies have shown, and therefore there is a quest for mediators that render trigeminal neurons hyperexcitable. This process may involve cytokines, in which case the authors' previous experience would be explained.

The study protocol is clear and robust. Inclusion criteria are a bit ambiguous. The authors do not detail the pain they expect their patients to have, and there is a concern that not all those eligible will have the same pain. Both naive cases of TGN and those suffering form recurrence after neurodestructive surgery may be recruited. The IASP definition does not differentiate well between typical and atypical forms of tic douloreux, and the authors would do well decide a priori on clear cut inclusion/exclusion criteria based on the specific characteristics of the pain description. Another issue to pay attention to is the history of remissions; many patients with trigeminal neuralgia experience long remissions before the condition becomes permanent. May patients will have discontinued carbamazepine because of problems with tolerability, and can be treated successfully
with other pharmacological agents.

The primary outcome measure, time to exit from trial, is very appropriate and applicable to a study of this type. By setting the criterion for improvement as being equivalent to the patient's impression of change in the highest category is commendable. The list of secondary variables is long but each item can be justified. It is not entirely clear how the investigators will quantitate the very essence of trigeminal pain, i.e., paroxysms. The design of the diary may be crucial; the patients are usually quite capable of accurately recording on the frequency and types of attacks (see, e.g., Zakrzewska et al, Pain, 1997). Attacks of pain should be defined; will a solitary jab count as an attack? Whether pain becomes less sensitive to external stimuli during the trial might be worth recording as well. Sample size calculations are based on reasonable assumptions. It is not clear what the authors mean by "controls".

This study is clearly designed to take place in a country with an established health insurance based method of health care delivery. The authors do not mention the specifics of the funding arrangements, but presumably within such a system, a research project of this kind can be conducted. There are no serious ethical concerns because of the "therapeutic failure design". Undoubtedly the authors will be able to address the concern that the patients may not receive approval from the funding authorities for future treatment with IVIG.

Competing interests:

None declared.