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LETTER TO THE EDITOR

Response to letter on European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of Guillain–Barré syndrome

Dear Editor,

We respond to the letter of Drs. Li and Lu regarding the European Academy of Neurology/Peripheral Nerve Society (EAN/PNS) Guideline on diagnosis and treatment of Guillain–Barré syndrome (GBS) [1]. Their question is why the GBS Guideline Task Force (TF) made a strong recommendation against the administration of a second course of intravenous immunoglobulins (IVIg; second immunoglobulin dose [SID]) in GBS patients with a poor prognosis.

This recommendation is based on the SID-GBS randomized clinical trial (RCT), the only available RCT that investigated this question [2]. In the EAN/PNS GBS Guideline, PICOs (Patient/Intervention/Control/Outcome) on intervention were subjected to GRADE (Grading of Recommendations Assessment, Development, and Evaluation) assessment, which enables the TF to make strong or weak recommendations for or against an intervention.

Drs. Li and Lu suggested that using the modified Erasmus GBS Outcome Score (mEGOS) on admission may recruit more patients who might potentially benefit from SID in the early course of disease, and additionally, that patients with high mEGOS (≥7; range = 0–12) in another study were found to benefit from intensive immunotherapy [3]. This retrospective study, however, did not report significant benefit of SID in this group of GBS patients, which is compatible with the results of the international observational SID (I-SID) study and with the SID-GBS RCT [2, 4]. No RCT, however, is perfect, and it is always possible that individual patients could have had benefit from a more intensive treatment. This, however, does not imply that such an intensive treatment should be applied, and especially not when this is associated with more serious adverse events (SAEs).

We agree that, although the GBS disability score at 4 weeks is most frequently used as primary outcome for RCTs in GBS, long-term outcome is also very important. Long-term outcomes were used as (secondary) endpoints in RCTs, including the SID-GBS trial. Unfortunately, none of these endpoints was in favour of SID.

Not all questions regarding IVIg retreatment of GBS patients with a poor prognosis have been elucidated with the SID-GBS trial. This study randomized GBS patients for SID or placebo when they had a poor prognosis based on mEGOS ≥ 6 at day 7–9, thus 2–4 days after finalizing a standard 5-day IVIg course. Even in an RCT, it is impossible to control for all potential relevant factors, but to limit imbalance, covariate adjustment has been used in the analysis of the SID-GBS study.

Both the recently validated mEGOS and a retrospective study from Japan showed that determination of the prognosis based upon mEGOS can appropriately be done at admission and after 1 week [3, 5]. It is important, however, to realize that individual patients can improve or deteriorate within the first week(s) after admission, and that the effect of IVIg may take some time to show. Therefore, the SID-GBS trial was designed so that patients were randomized for SID or placebo when they had a poor prognosis (≥6) based on mEGOS assessed shortly after a standard course of IVIg. To re-treat early, based on the use of a prognostic model, seemed attractive because it was considered inappropriate to wait longer (until week 3 or 4) once it becomes clear that a patient is in a very poor neurological condition, when treatment is less effective [6]. Selecting GBS patients with a poor prognosis shortly after a standard IVIg course likely avoids overuse of IVIg. This is relevant because IVIg is expensive, there is a worldwide shortage of IVIg, and reloading a patient with full IVIg course shortly after a first standard IVIg course potentially induces more SAEs.

We agree that it has not been investigated whether a short (2–4 days) delay after the end of a standard IVIg course might have contributed to the neutral effects found in the SID-GBS study. However, as this trial did not find any positive effect of SID during a 26-week follow-up period, no subgroup could be identified that did better after SID, and more SID-treated patients developed severe SAEs, the GBS Guideline TF decided to make a strong recommendation against giving SID to GBS patients with a poor prognosis.

It is still not clear why GBS patients with a poor prognosis developed more SAEs when treated with SID. Whether this is due to the severity of disease, why these SAEs seem not directly related to the individual IgG levels, or whether this is due to a combination of factors is currently still unclear. The most relevant finding, however, is that SAEs occurred more frequently in this group of GBS patients treated with SID.

Despite IVIg, GBS is currently still a severe disease in many patients. It seems unlikely that shortening the delay of only a few days between the end of the first standard IVIg course and starting SID

caused the negative results of the SID-GBS trial. The TF believes that there are strong arguments against starting SID in GBS patients with a poor prognosis early in the course of disease. It is time to look ahead for new treatments that hopefully will show clear benefit alone or in combination with IVIg. Fortunately, these studies are currently ongoing.

AUTHOR CONTRIBUTIONS

Pieter A. van Doorn: Writing – review and editing; writing – original draft. **Peter Y.K. Van den Bergh:** Writing – review and editing. **Robert D. M. Hadden:** Writing – review and editing.

CONFLICT OF INTEREST STATEMENT

Pieter A. van Doorn is the Principle Investigator (PI) of the SID-GBS trial (ref 2). The other authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Pieter A. van Doorn[1]
Peter Y. K. Van den Bergh[2]
Robert D. M. Hadden[3]
on behalf of the GBS Guideline Task Force

[1]*Department of Neurology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands*
[2]*Neuromuscular Reference Centre, Department of Neurology, University Hospital Saint-Luc, Brussels, Belgium*
[3]*Department of Neurology, King's College Hospita, London, UK*

Correspondence
Pieter A. van Doorn, Department of Neurology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands.
Email: p.a.vandoorn@erasmusmc.nl

ORCID

Pieter A. van Doorn https://orcid.org/0000-0003-2584-3357
Peter Y. K. Van den Bergh https://orcid.org/0000-0003-1954-4617
Robert D. M. Hadden https://orcid.org/0000-0002-9702-0256

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