

Disputes & Debates: Editors' Choice

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Editors' Note: Intravenous Immunoglobulin Therapy in Patients With Painful Idiopathic Small Fiber Neuropathy

In "Intravenous Immunoglobulin Therapy in Patients With Painful Idiopathic Small Fiber Neuropathy," Geerts et al. report no significant difference in Pain Intensity Numerical Rating Scale score for patients with idiopathic small fiber neuropathy (I-SFN) 12 weeks after randomized administration of IVIG or placebo.

Song and Xu comment that the IVIG-dosing regimen and pain evaluation used in this study differs from that of prior studies which found IVIG to be effective for patients with immune-mediated SFN; they suggest a follow-up study comparing regimens. On behalf of the authors, Faber replies that there was no difference between these regimens in patients with inflammatory neuropathies and that while they selected to administer IVIG over 2 days to minimize treatment burden, the total dose is the same as would be given over 5 days, making it unlikely there would be any difference in outcome if the IVIG was administered over a longer period. She further notes that it would be practically and ethically challenging to perform a follow-up study by comparing regimens, given the negative findings.

Gemignani notes that it is important to recognize that patients with nonlength-dependent SFN were excluded from this study but that they may (1) have a distinct evolution of pain compared with patients with other types of SFNs and (2) be more responsive to IVIG because of the association of this type of neuropathy with autoimmune conditions. Wilder-Smith and Spoenclin also reinforce the potential for IVIG to benefit patients with autoimmune SFN and ask the authors to provide additional data on the number of patients who were excluded because of autoimmune disease and perform subgroup analysis based on symptom duration, given that patients with early initiation of IVIG may be more likely to improve with IVIG. Faber clarifies that 16% of patients who were screened for enrollment were excluded because of known autoimmune conditions but does not comment on the relationship between pain intensity in patients with shorter duration of symptoms after treatment with IVIG vs placebo. Faber agrees that additional research is needed to evaluate the role of IVIG in patients with nonlength-dependent SFN, particularly given that open-label studies show IVIG was beneficial in this population. However, she emphasizes that before their randomized investigation, there were also case studies that demonstrated IVIG to be beneficial in SFN, which reinforces the importance of double-blind randomized trials.

Ariane Lewis, MD, and Steven Galetta, MD
Neurology® 2021;97:791. doi:10.1212/WNL.0000000000012707

Reader Response: Intravenous Immunoglobulin Therapy in Patients With Painful Idiopathic Small Fiber Neuropathy

Pu Song (Suzhou City, China) and Xingshun Xu (Suzhou City, China)
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We read with great interest the recent article by Margot Geerts et al.¹ The authors evaluated the efficacy of IV immunoglobulin (IVIG) in patients with idiopathic small fiber neuropathy (I-

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SFN). Immunologic mechanisms may be involved in the pathophysiology of some I-SFN.² Previous studies showed that IVIG treatment is effective against immune-mediated SFN³⁻⁵; however, they found that IVIG treatment was not effective in 30 patients with I-SFN. Previous studies on SFN used IVIG for at least 5 consecutive days, and the pain was evaluated immediately after treatment.³⁻⁵ Alternatively, IVIG was administered in this study for 2 consecutive days with a 3-week interval for 4 rounds based on a regimen for chronic inflammatory demyelinating polyneuropathy but not for SFN. The pain was evaluated at weeks 1 and 12 and month 6 after the first dose.¹ Therefore, if the authors followed the protocols for SFN as in previous studies,³⁻⁵ they may have different conclusions on IVIG efficacy. The authors should compare the efficacy of 2 regimens about IVIG usage.

1. Geerts M, de Greef BTA, Sopacua M, et al. Intravenous immunoglobulin therapy in patients with painful idiopathic small fiber neuropathy. *Neurology*. 2021;96(20):e2534-e2545.
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Author Response: Intravenous Immunoglobulin Therapy in Patients With Painful Idiopathic Small Fiber Neuropathy

Margot Geerts (Maastricht, the Netherlands), Bianca T.A. de Greef (Maastricht, the Netherlands), Maurice Sopacua (Maastricht, the Netherlands), Sander M.J. van Kuijk (Maastricht, the Netherlands), Janneke G.J. Hoeijmakers (Maastricht, the Netherlands), Catharina G. Faber (Maastricht, the Netherlands), and Ingemar S.J. Merkies (Maastricht, the Netherlands)
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We would like to respond to the comments made by Pu Song and Xingshun Xu about the chosen administration of IV immunoglobulin (IVIG), which is based on a regimen for chronic inflammatory demyelinating polyneuropathy (CIPD). These authors also expressed doubts about our conclusion that IVIG was not effective in patients with painful with idiopathic small fiber neuropathy (I-SFN).

Our study was designed as a RCT, which has been partly applied and published previously in the ICE-trial,² in which we hypothesized that immunological mechanisms may play a role in patients with I-SFN. The regimen of 2 days of 1 g of IVIg, totaling in a dose of 2 g, has been shown to be comparable with 5 days of 0.4 g of IVIg in patients with inflammatory neuropathies. Therefore, we have chosen the 2-day regimen because this decreases the treatment burden to patients considerably.³ Because the total dose is the same in both regimens, it is unlikely that this has caused a lack of effect. Indeed, to rule out the possibility, both regimens should be compared. However, as the trial was negative, it will be not very easy to run such a study.

1. Geerts M, de Greef BTA, Sopacua M, et al. Intravenous immunoglobulin therapy in patients with painful idiopathic small fiber neuropathy. *Neurology*. 2021;96(20):e2534-e2545.
2. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial [published correction appears in *Lancet Neurol*. 2008 Sep;7(9):771]. *Lancet Neurol*. 2008;7(2):136-144.
3. de Greef BT, Geerts M, Hoeijmakers JG, Faber CG, Merkies IS. Intravenous immunoglobulin therapy for small fiber neuropathy: study protocol for a randomized controlled trial. *Trials*. 2016;17(1):330.

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Reader Response: Intravenous Immunoglobulin Therapy in Patients With Painful Idiopathic Small Fiber Neuropathy

Franco Gemignani (Parma, Italy)

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Geerts et al.¹ showed, in a randomized controlled trial, that intravenous immunoglobulin (IVIg) has no significant effect on pain in patients with painful idiopathic small fiber neuropathy (SFN). A potential exception is represented by patients with idiopathic SFN with a nonlength-dependent (NLD) phenotype, as they were excluded by the design of the study.

Some considerations allow the possibility that NLD-SFN could be responsive to IVIg therapy. First, NLD-SFN is more often associated with autoimmune conditions.^{2,3} Assuming that immunologic mechanisms—potentially responsive to IVIg—contribute to patients with idiopathic SFN, these conditions would more probably present with a NLD-SFN pattern. NLD-SFN is also related to ganglionopathy, with the primary site of autoimmune damage at the level of the small sensory neurons of the dorsal root ganglia (DRG).⁴ DRG are supplied by fenestrated capillaries with no tight blood–nerve barrier,⁵ and thus, they could offer a privileged window permissive to therapeutic agents targeting the affected sites. Furthermore, pain mechanisms might differ in distal SFN and NLD-SFN, because of different sites of primary damage.²

Further studies focused on NLD-SFN would be needed to definitively exclude a possible therapeutic role of IVIg in painful idiopathic SFN.

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Author Response: Intravenous Immunoglobulin Therapy in Patients With Painful Idiopathic Small Fiber Neuropathy

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We would like to respond to the comments made by Mr. Franco Gemignani on our article¹ regarding the nonlength-dependent small fiber neuropathy (NLD-SFN) phenotype as a potential condition that could benefit from intravenous immunoglobulin therapy (IVIg). We fully agree that future studies in NLD-SFN would be needed to determine whether IVIg would have a therapeutic role in these conditions. There are some open-label clinical studies suggesting a potential therapeutic role,^{1,2} as well as distal SFN case-studies showing a positive effect of IVIg, whereas the results of our RCT showed that IVIg treatment had no significant effect on pain in patients with painful idiopathic SFN. This underlines the pitfalls of case reports or open case studies and the importance of double-blind randomized trials.

Author disclosures are available upon request (journal@neurology.org).

1. Geerts M, de Greef BTA, Sopacua M, et al. Intravenous immunoglobulin therapy in patients with painful idiopathic small fiber neuropathy. *Neurology*. 2021;96(20):e2534-e2545.
2. Liu X, Treister R, Lang M, Oaklander AL. IVIg for apparently autoimmune small-fiber polyneuropathy: first analysis of efficacy and safety. *Ther Adv Neurol Disord*. 2018;11:1756285617744484.

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Reader Response: Intravenous Immunoglobulin Therapy in Patients With Painful Idiopathic Small Fiber Neuropathy

Einar Wilder-Smith (Luzern, Switzerland) and Julia Spoendlin (Basel, Switzerland)
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We read with interest the results of the first RCT evaluating the efficacy of intravenous immunoglobulin therapy (IVIg) in patients with idiopathic small fiber neuropathy (I-SFN) and congratulate the authors for this important trial.¹

However, the results of this trial may discourage the use of IVIG in patients with SFN who could greatly profit from IVIG. Patients with I-SFN represent a heterogeneous group with different underlying pathomechanisms. IVIG, which is designed for autoimmune and inflammatory conditions, has been documented to be successfully used in a retrospective study of 55 patients with I-SFN and more than 20 case reports.^{2,3}

The following characteristics have been associated with autoimmune involvement in I-SFN: acute onset, coexisting autoimmune disease, persistent hand pain, younger age, and/or non-length dependent symptoms.²⁻⁴ It is important to better characterize this study's participants because those who are most likely to benefit from the treatment may have been excluded.

Can the authors provide a PRISMA-style flowchart including the number of ineligible patients with I-SFN due to either a concomitant autoimmune disease, such as Sjogren or celiac disease, or nonlength dependent pain patterns? Similarly, it would be helpful to know the proportions of acute SFN onset, hand involvement, other autoimmune comorbidities, and earlier immunotherapy. Finally, a subgroup analysis of I-SFN duration would help, as short duration may improve outcomes of immunotherapy.³

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Author Response: Intravenous Immunoglobulin Therapy in Patients With Painful Idiopathic Small Fiber Neuropathy

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We would like to respond to the comments made by Drs. Wilder-Smith and Spoendlin on our study¹ related to the heterogeneous group of patients with idiopathic small fiber neuropathy (I-

SFN), who might benefit from intravenous immunoglobulin (IVIg) therapy. Before study entry, all patients had a diagnostic SFN workup, which includes tests for several associated conditions, as mentioned in the inclusion criteria.¹ Of 257 patients, there were 193 patients who did not meet the inclusion criteria, 41 of which (16%) were excluded because of known autoimmune conditions, which is in line with previous findings.² Future studies are needed to definitely determine whether IVIg may have a therapeutic role in the treatment of autoimmune conditions that cause SFN. There are some open-label clinical studies suggesting a potential therapeutic role,^{3,4} but stronger evidence from a randomized study is needed. Our RCT showed that IVIg treatment had no significant effect on pain in patients with painful I-SFN and should therefore be discouraged.

1. Geerts M, de Greef BTA, Sopacua M, et al. Intravenous immunoglobulin therapy in patients with painful idiopathic small fiber neuropathy. *Neurology*. 2021;96(20):e2534-e2545.
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CORRECTIONS

Prospective Quantification of CSF Biomarkers in Antibody-Mediated Encephalitis

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In the article “Prospective Quantification of CSF Biomarkers in Antibody-Mediated Encephalitis” by Day et al.,¹ the second author’s name should be listed as “Melanie L. Yarbrough.” The authors regret the error.

Reference

1. Day GS, Yarbrough MY, Körtvelyessy P, et al. Prospective quantification of CSF biomarkers in antibody-mediated encephalitis. *Neurology*. 2021;96(20):e2546-e2557.

Cross-Sectional Profile of Most Bothersome Problems as Reported Directly by Individuals With Parkinson’s Disease (2697)

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In the AAN Annual Meeting abstract “Cross-Sectional Profile of Most Bothersome Problems as Reported Directly by Individuals With Parkinson’s Disease (2697)” by Vinikoor-Imler et al.,¹ the authors should be listed as follows: Feiby Nassan, Lakshmi Arbatti, Abhishek Hosamath, Lisa Vinikoor-Imler, Inbal Sapir, Julia Shirvan, Nancy Maserejian, Ira Shoulson. The AAN scientific programming team regrets the error.

Reference

1. Vinikoor-Imler L, Arbatti L, Hosamath A, et al. Cross-sectional profile of most bothersome problems as reported directly by individuals with Parkinson’s disease (2697). *Neurology*. 2021;96(15 supplement):2697.

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