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Antibody Response after COVID-19 Vaccination in Intravenous Immunoglobulin-Treated Immune Neuropathies

An Observational Study

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Abstract

Background

This study assessed the prevalence of anti-SARS-CoV-2 antibodies in therapeutic immunoglobulin and their impact on serological response to COVID-19 mRNA vaccine in patients with intravenous immunoglobulin (IVIg)-treated chronic immune neuropathies.

Methods

Forty-six samples of different brands or lots of IVIg or subcutaneous IgG (SCIg) were analyzed for anti-SARS-CoV-2 IgG using ELISA and chemiluminescent microparticle immunoassay (CMIA). Blood sera from 16 patients with immune neuropathies were prospectively analyzed for anti-SARS-CoV-2 IgA, IgG, and IgM before and one week after IVIg infusion subsequent to consecutive COVID-19 mRNA vaccine doses and after 12 weeks. These were compared to 42 healthy subjects.

Results

Twenty-four (52%) therapeutic immunoglobulin samples contained anti-SARS-CoV-2 IgG. All patients with immune neuropathies (mean age 65 ± 16 years, 25 % female) were positive for anti-SARS-CoV-2 IgG after COVID-19 vaccination. Anti-SARS-CoV-2 IgA titers significantly decreased 12-14 weeks after vaccination (p=0.02), IgG titers remained stable (p=0.2). IVIg did not significantly reduce intra-individual anti-SARS-CoV-2 IgA/IgG serum titers in immune neuropathies (p=0.69). IVIg-derived anti-SARS-CoV-2 IgG did not alter serum anti-SARS-CoV-2 IgG decrease after IVIg administration (p=0.67).

Conclusions

Our study indicates that IVIg does not impair the antibody response to COVID-19 mRNA vaccine in a short-term observation, when administered a minimum of two weeks after each vaccine dose. The infusion of current IVIg preparations that contain anti-SARS-CoV-2 IgG does not significantly alter serum anti-SARS-CoV-2 IgG titers.

Introduction

The use of therapeutic immunoglobulin, either administered intravenously (IVIg) or subcutaneously (SCIg), is an established therapy for immune neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP), or multifocal motor neuropathy (MMN) [1–4]. IVIg contains IgG from more than 3000 healthy donors and some IVIg preparations manufactured before the COVID-19 pandemic may contain cross-reactive IgG with a binding capacity to SARS-CoV-2 *in vitro* but lacking neutralizing effect *in vivo* [5–10]. Since 2020, it is conceivable but not known to what extent IVIg preparations manufactured during the COVID-19 pandemic may contain specific anti-SARS-CoV-2 IgG.

In IVIg dependent autoimmune conditions, patients and caregivers articulated concerns about general and specific vaccine efficacy due to a potential neutralizing activity of IVIg [11,12], that may lead to a diminished seroconversion rate as observed in vaccinations with live attenuated viruses [13]. Furthermore, IVIg promotes anti-inflammatory immune pathways, i.e. activation of inhibitory Fc gamma receptor II b (FcγRIIb) on B cells [14–16], which might reduce vaccine-stimulated anti-SARS-CoV-2 antibody production.

In order to assess the efficacy and safety of a co-administration of IVIg and COVID-19 mRNA vaccine, we I) evaluated IVIg-derived anti-SARS-CoV-2 IgG titers in lots of different IVIg and SCIg brands produced during the COVID-19 pandemic, and II) prospectively analyzed antibody generation against SARS-CoV-2 after COVID-19 vaccination in IVIg treated patients with immune neuropathies and healthy subjects between March and July 2021.

Methods

Study design and participants

Sixteen patients with immune neuropathies (14 with CIDP, two with MMN) were prospectively enrolled between March and July 2021 at the Department of Neurology of University Hospital of Cologne. Inclusion criteria were confirmed CIDP or MMN (based on the 2010 EFNS/PNS criteria [17]) on regular IVIg treatment (1 g/kg bodyweight every four to five weeks), exclusion criteria were acute systemic infections, intake of immunosuppressants (i.e. cyclophosphamide or azathioprine) and monoclonal antibodies (i.e. rituximab), or previous COVID-19 infection. All participants underwent regular SARS-CoV-2 PCR testing and had no clinical history of COVID-19.

Paired serum samples before and one week after immunoglobulin treatment were collected from n=7 patients 22 ± 4 days after the first, and of n=15 patients 17 ± 5 days after the second dose of COVID-19 vaccine. The scheduled time interval between each vaccine dose and IVIg infusion was based on expert opinions, suggesting an interval of a minimum of two weeks between each vaccine dose and IVIg infusion [18]. The mean interval between the first and the second dose of COVID-19 vaccine was 4 ± 1 weeks. An additional follow-up visit was encompassed 12 weeks after the first dose of COVID-19 vaccine (**Fig. 1**). All patients received a COVID-19 mRNA vaccine. A sample of the individually administered IVIg lot was also collected directly before IVIg infusion for anti-SARS-CoV-2 IgG testing.

Serum anti-SARS-CoV-2 antibody titers were compared to a cohort of 42 healthy subjects, recruited from staff at the local Institute of Virology, that was vaccinated with a COVID-19 mRNA vaccine and provided serum samples in comparable intervals as the immune neuropathy patients. Blood samples were collected 15 days (for IgA and IgG ELISA), or 24 days (for IgG and IgM chemiluminescent microparticle immunoassay (CMIA)) after the first vaccine dose, 14 days after the second dose and at a mean of 14 ± 1 weeks later (**Fig. 1**). To exclude age-related differences in anti-SARS-CoV-2 IgG generation, the cohorts were age-matched in a second step by selection of age-matched subjects and excluding a statistically significant age difference (mean age after the first vaccine dose [patients vs. healthy subjects]: 60 vs. 58 years; after the second dose: 57 vs. 57 years; at follow-up: 69 vs. 61 years).

A total of 40 IVIg and 6 SCIg samples (Gamunex®: 5 lots, Iqymune®: 3 lots, Privigen®: 2 lots, Octagam®: 6 lots, Hizentra®, SCIg: 5 lots), were prospectively collected between March and July 2021 to examine anti-SARS-CoV-2 IgG titers by ELISA and CMIA.

IVIg-derived anti-SARS-CoV-2 IgG titers were correlated with serum anti-SARS-CoV-2 antibody decrease after IVIg infusion to examine their impact on IVIg-related interactions with COVID-19 vaccination.

Immunoassays

Anti-SARS-CoV-2 IgG and IgA ELISA

Samples were analyzed immediately after collection by the Euroimmun anti-SARS-CoV-2 IgG and IgA ELISA (enzyme-linked immunosorbent assay), targeting the SARS-CoV-2 S1 spike protein domain on the Euroimmun Analyzer I (Euroimmun Diagnostik, Lübeck, Germany), according to the manufacturer's protocol. A sample-to-calibrator ratio (S/CO ratio) was calculated to allow a semi-quantitative assessment of antibody titers. A S/CO ratio of ≥ 1.1 was considered positive with ≥ 0.8 - < 1.1 considered borderline and < 0.8 considered negative.

Anti-SARS-CoV-2 IgG and IgM chemiluminescent microparticle immunoassay (CMIA)

Chemiluminescent microparticle immunoassay (CMIA) provided by Abbot (SARS-CoV-2 IgG II Quant and SARS-CoV-2 IgM) on the Alinity i system (Abbott, Abbott Park, IL, United States) was performed for quantitative assessment of anti-SARS-CoV-2 IgG and qualitative assessment of anti-SARS-CoV-2 IgM within therapeutic immunoglobulin and serum samples, using the SARS-CoV-2 S1 spike protein receptor binding domain (RBD) as specific target structure according to the manufacturer's protocol. Anti-SARS-CoV-2 IgG values ≥ 7.1 BAU/ml (binding antibody units per milliliter) were considered positive. Qualitative assessment of anti-SARS-CoV-2 IgM was performed calculating a ratio (S/C ratio) of sample and calibrator solution relative light units. A S/C ratio of ≥ 1.0 was considered positive.

Statistical analysis

GraphPad PRISM 9.2.0 software was used for statistical analysis. Categorical variables were calculated as frequency distribution or percentages. Continuous variables were calculated as mean with standard deviation and range. Between-group comparisons for continuous variables were carried out by testing for Gaussian distribution using D'Agostino and Pearson omnibus normality test before testing for statistical difference and significance using either Mann-Whitney U test or unpaired t test when comparing two groups. The Kruskal-Wallis test or one-way ANOVA followed by Dunn's multiple comparisons test was performed to compare three or more groups with continuous variables. Correlation analyses were carried out by calculating the Spearman correlation coefficient and linear regression. A p-value < 0.05 was considered statistically significant.

Ethics approval and consent to participate

All patients with immune neuropathies gave written informed consent for immunologic examinations of their blood sera before and after immunoglobulin therapy. The University of Cologne Ethics Committee approved the study (approval reference number: 19-1662_1) registered in the German clinical trial register (DRKS00025759). As data from healthy subjects were pooled and thus anonymized immediately after collection, no written informed consent was necessary for study participation in this cohort. This study conforms with the World Medical Association Declaration of Helsinki and was carried out per the local laws at the University Hospital of Cologne.

Results

Anti-SARS-CoV-2 IgG in therapeutic immunoglobulin

Of 40 IVIg samples (Gamunex®: 5 lots, Iqymune®: 3 lots, Privigen®: 2 lots, Octagam®: 6 lots) and six SCIg samples (Hizentra®: 5 lots) collected between March and July 2021, 24/46 samples (52 %, CMIA), and 21/38 samples (55 %, ELISA) showed relevant IgG reactivity against SARS-CoV-2 (**Fig. 2 A-B**). All 46 samples were tested for anti-SARS-CoV-2 IgG using CMIA, whereas anti-SARS-CoV-2 IgG ELISA was performed for 38/46 samples.

Anti-SARS-CoV-2 IgG titers were significantly higher in Gamunex® than in other immunoglobulin preparations in both assays (p<0.0001; **Fig. 2 A-B**). Five of eleven (ELISA), or 8/13 (CMIA) Octagam® samples, and 4/6 (ELISA) or 2/6 (CMIA) Hizentra® samples contained anti-SARS-CoV-2 IgG. Apart from one Iqymune® sample showing reactivity against SARS-CoV-2 in the ELISA, Iqymune® and Privigen® did not reveal measurable titers of anti-SARS-CoV-2 IgG (**Fig. 2 A-B**).

Anti-SARS-CoV-2 IgG titers varied between immunoglobulin brands and lots and even within the same lot, i.e. in one Gamunex® (*B3GJC00453*), and in one Hizentra® lot (*P100212687*), only one of two tested samples contained anti-SARS-CoV-2 IgG.

Serum anti-SARS-CoV-2 antibody titers in patients treated with IVIg

Anti-SARS-CoV-2 IgA: Serum anti-SARS-CoV-2 IgA titers did not significantly differ between patients (mean age 65 ± 16 years, 25 % female) and healthy subjects (mean age 42 ± 13 years, 83 % female) after the first dose of COVID-19 vaccine (S/CO ratio: 4.3 ± 3.8 vs. 7.6 ± 1.7, p=0.09; **Fig. 3 A**). After IVIg treatment, anti-SARS-CoV-2 IgA titers were significantly lower when compared to healthy subjects (p=0.009), but not when compared to baseline titers (p=0.45; **Fig. 3 A**). Anti-SARS-CoV-2 IgA titers significantly increased after the second dose of COVID-19 vaccine (p=0.002) and IVIg administration did not significantly alter this effect. Serum anti-SARS-CoV-2 IgA titers significantly decreased 12 weeks after the first vaccine dose (p=0.02; **Fig. 3 A**).

Anti-SARS-CoV-2 IgG: Anti-SARS-CoV-2 IgG titers were significantly lower in patients after the first vaccine dose compared to healthy subjects when assessed by ELISA (S/CO ratio: 3.1 ± 2.3 vs. 5.8 ± 1.6, p=0.011; **Fig. 3 B**). Like IgA antibody titers, anti-SARS-CoV-2 IgG titers significantly increased after the second vaccine dose and remained stable after 12 weeks (p=0.2; **Fig. 3 B**).

Anti-SARS-CoV-2 IgG CMIA was performed after the first and second COVID-19 vaccine dose in healthy subjects in contrast to anti-SARS-CoV-2 IgA and IgG ELISA, which were only performed after the first vaccine dose. Therefore, by CMIA, anti-SARS-CoV-2 IgG titers were compared after both vaccine doses (**Fig. 3 C-D**).

Serum anti-SARS-CoV-2 IgG titers measured by CMIA were significantly lower in patients compared to healthy subjects after the first vaccine dose. IVIg treatment had no significant effect on antibody response (binding antibody units per milliliter [immune neuropathy patients vs. healthy subjects]: 615 ± 1509 BAU/ml vs. 627 ± 577 BAU/ml, p=0.71; **Fig. 3 C**). After the second vaccine dose, anti-SARS-CoV-2 IgG titers increased in healthy subjects (3776 ± 2376 BAU/ml; p<0.0001) and in patients (1670 ± 914 BAU/ml, p=0.007; **Fig. 3 C**). Also, anti-SARS-CoV-2 IgG titers were significantly lower in patients than in healthy subjects after the second vaccine dose (p=0.003, **Fig. 3 C**). Age matching vanished these inter-group differences after the first vaccine dose, whereas the difference persisted after the second vaccine dose (p<0.0001) without being influenced by IVIg (p=0.69, **Fig. 3 D**). Anti-SARS-CoV-2 IgG titers did not significantly differ between both cohorts at follow-up ([immune neuropathy patients vs. healthy subjects]: 553 ± 434 BAU/ml vs. 2518 ± 2476 BAU/ml, p=0.11). Furthermore, no significant difference was seen between follow-up anti-SARS-CoV-2 IgG titers compared to those after the second vaccine dose in both cohorts (p=0.07; **Fig. 3 C-D**).

Anti-SARS-CoV-2 IgM: Anti-SARS-CoV-2 IgM titers were compared by CMIA after the second dose of COVID-19 vaccine. More healthy subjects than patients showed anti-SARS-CoV-2 IgM (10/29 subjects [34 %] vs. 1/5 patients [20 %]; **Table 1**).

IVIg-derived anti-SARS-CoV-2 IgG does not impact serum anti-SARS-CoV-2 IgG titers

IVIg infusion led to a non-significant decrease of serum anti-SARS-CoV-2 IgG titers in all patients with immune neuropathies (**Fig. 3 B-D**).

The percentual serum anti-SARS-CoV-2 IgG titer decrease (one week after IVIg infusion compared to before IVIg) after the second COVID-19 vaccine dose was calculated and then correlated with the amount of IVIg-derived anti-SARS-CoV-2 IgG within the individually infused IVIg sample, to evaluate whether IVIg-derived anti-SARS-CoV-2 IgG influenced serum anti-SARS-CoV-2 IgG titers after IVIg infusion.

No significant correlation was found between IVIg-derived anti-SARS-CoV-2 IgG and serum anti-SARS-CoV-2 IgG decrease after IVIg infusion after the second vaccine dose (Spearman r = -0.14, p=0.67), indicating that anti-SARS-CoV-2 IgG derived from currently available IVIg preparations did not significantly impact serum anti-SARS-CoV-2 IgG titers.

Tolerability of a co-administration of IVIg and COVID-19 mRNA vaccine

No abnormalities in IVIg-related side effects were reported from immune neuropathy patients after both doses of COVID-19 mRNA vaccine. Furthermore, no clinical deterioration was observed in immune neuropathy patients after both COVID-19 vaccine doses.

Discussion

In contradiction to earlier observations that IVIg did not contain significant amounts of specific anti-SARS-CoV-2 IgG in 2020 [10,19], our study proves that more than half of more recently manufactured therapeutic immunoglobulin contains anti-SARS-CoV-2 IgG. *In vitro* IgG cross-reactivity against other, seasonal human corona viruses generally has to be considered [9]. However, the combination of two established analysis techniques (ELISA and CMIA) with conclusive results and CMIA's high specificity for antibodies targeting SARS-CoV-2 specific S1 spike protein receptor binding domain (RBD)[20–22] makes us confident that the observed antibody titers are derived from specific anti-SARS-CoV-2 IgG. Also, all threshold levels for antibody positivity were well established by earlier studies [21,23,24]. A shorter manufacturing process or, as demonstrated for other pathogens [25], the acquisition of plasma from COVID-19 high-incidence regions resulting in more anti-SARS-CoV-2 seropositive donors could explain anti-SARS-CoV-2 IgG positive IVIg. Since anti-SARS-CoV-2 seropositivity is increasing worldwide [26], we anticipate that also the number of IVIg and SCIg lots containing anti-SARS-CoV-2 IgG will rise in the future. In two cases, anti-SARS-CoV-2 IgG content varied significantly within the same immunoglobulin lot, indicating that manufacturing procedures might also influence the individual content of anti-SARS-CoV-2 IgG.

In patients with IVIg dependent immune neuropathies who received COVID-19 mRNA vaccine, IVIg treatment did not alter the serum anti-SARS-CoV-2 antibody response. Patients receiving IVIg did not report abnormalities of IVIg-related side effects after COVID-19 vaccination and no relevant clinical deterioration was observed post vaccination, providing critical information regarding the safety of IVIg administration a minimum of two weeks after COVID-19 vaccination.

Anti-SARS-CoV-2 IgG serum levels after each vaccine dose were in line with a recent study analyzing serum samples of 145 vaccinated subjects receiving either Pfizer-BioNTech or Moderna mRNA COVID-19 vaccine in intervals comparable to our study and using the same CMIA [21]. In this study, anti-SARS-CoV-2 IgG titers differed from titers of healthy subjects and immune neuropathy patients in our study as follows: after the first vaccine dose: 315 [range 0-

6274] BAU/ml vs. 627 ± 577 [range 50-2179] BAU/ml vs. 615 ± 1509 [range 10-4038] BAU/ml; after the second vaccine dose: 2595 [range 1665-3089] BAU/ml vs. 3776 ± 2376 [range 228-9499] BAU/ml vs. 1670 ± 914 [range 404-3449] BAU/ml) [21].

Long-term immunomodulatory effects of IVIg, like induction of inhibitory Fc gamma receptors on B cells [14], or, as observed in a recent study on rheumatic diseases and COVID-19 vaccination [27], altered efficacy of the immune system due to autoimmunity, could generally explain our finding that anti-SARS-CoV-2 IgG serum titers remained lower in immune neuropathy patients than in age-matched healthy subjects after the second COVID-19 vaccine dose. Furthermore, sex-related differences in anti-SARS-CoV-2 IgG generation have to be considered a confounding factor, possibly exaggerating the difference between immune neuropathy patients (25 % female) and healthy subjects (83 % female), as a recent study demonstrated that female sex is associated with higher anti-SARS-CoV-2 antibody titers after COVID-19 mRNA vaccination [28]. However, all patients showed anti-SARS-CoV-2 IgG titers far above the cut-off for positivity and most within the range of healthy subjects without significant difference compared to healthy subjects at follow-up. Thus, taking into account that serum anti-SARS-CoV-2 antibody titers only reflect one surrogate marker for vaccine response, as other immune effectors like T cells are also involved in the development of immunity against COVID-19 [29,30], our data suggest a sufficient response to COVID-19 mRNA vaccine in patients with immune neuropathies. This is also supported by the fact that none of the immune neuropathy patients developed COVID-19 until July 2021. To our knowledge our study is the first that studied post-vaccine antibody response in IVIg dependent immune neuropathies [18].

Furthermore, the kinetics of anti-SARS-CoV-2 IgA and IgM were in line with previous studies, confirming a serum anti-SARS-CoV-2 IgA decrease 12 weeks after the last SARS-CoV-2 antigen exposition [21,31]. Differences in the detection of anti-SARS-CoV-2 IgG between ELISA and CMIA might be derived from a higher sensitivity of anti-SARS-CoV-2 IgG ELISA at lower IgG concentrations and IgG cross-reactivity leading to positive results in ELISA, but unlikely in CMIA [9,21,32].

Whether anti-SARS-CoV-2 IgG antibody response to vector-based vaccines differs from mRNA vaccines has to be examined in future studies. A small study in dialysis patients did not report significant differences after the first COVID-19 vaccine dose between Pfizer-BioNTech and Astra Zeneca COVID-19 vaccines [33].

Previous case reports indicated therapeutic efficacy of IVIg in severe COVID-19, assuming an immunomodulatory effect by alleviating COVID-19-related cytokine storm [34,35]. As treatment with convalescent plasma containing anti-SARS-CoV-2 IgG proved effective in severe COVID-19 via direct neutralization of SARS-CoV-2 [36,37], the potential of anti-SARS-CoV-2 IgG enriched IVIg to neutralize SARS-CoV-2 was previously discussed [38].

Our study is the first to systematically examine the impact of IVIg-derived anti-SARS-CoV-2 IgG on anti-SARS-CoV-2 serum IgG titers in a cohort of patients with immune neuropathies.

As serum anti-SARS-CoV-2 IgG titers neither increased after IVIg infusion nor correlated with IVIg-derived anti-SARS-CoV-2 IgG content, it appears unlikely that the amount of anti-SARS-CoV-2 IgG within currently available IVIg preparations is sufficient to significantly neutralize SARS-CoV-2 *in vivo*. Future studies including IgG neutralization assays are warranted to evaluate whether further enrichment of IVIg preparations with anti-SARS-CoV-2 IgG might significantly alter this effect.

Limitations of our study are its observational character and a relatively small cohort size especially within the immune neuropathy cohort, which was mainly derived from the fact that our study was conducted during a COVID-19 lockdown in Germany, causing difficulties in the follow-up of patients, as some patients wished to reduce hospital appointments to a minimum during this period. Furthermore, we did not perform IgG neutralization assays, which would be of interest for future studies to further evaluate the *in vivo* neutralizing potential of IVIg-derived anti-SARS-CoV-2 IgG.

Conclusions

Our study indicates that IVIg does not impair the antibody response to COVID-19 mRNA vaccine in a short-term observation and when administered a minimum of two weeks after vaccination. However, long-term immunomodulatory effects of IVIg, or altered immune efficacy in immune neuropathies, might alleviate vaccine response. Furthermore, currently available IVIg contains anti-SARS-CoV-2 IgG in amounts that are unlikely to exert relevant neutralizing effects on SARS-CoV-2 *in vivo*. It can be assumed that the frequency and amount of anti-SARS-CoV-2 IgG in future therapeutic immunoglobulin preparations might increase due to increasing numbers of seropositive donors with the need to systematically examine their neutralizing potential in larger studies.

List of abbreviations

BAU/ml = binding antibody units per milliliter; **CIDP** = chronic inflammatory demyelinating polyneuropathy; **CMIA** = chemiluminescent microparticle immunoassay; **COVID-19** = coronavirus disease 19; **ELISA** = enzyme-linked immunosorbent assay; **IgA** = immunoglobulin A; **IgG** = immunoglobulin G; **IgM** = immunoglobulin M; **IVIg** = intravenous immunoglobulin; **MMN** = multifocal motor neuropathy; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **SCIg** = subcutaneous immunoglobulin. **S/CO ratio** = sample-to-calibrator ratio.

Declarations

Consent for publication

All patients with immune neuropathies gave their consent for the publication of our results. As data from the healthy subjects were anonymized, no specific consent for publication was necessary in this cohort.

Availability of data and materials

The data of this study are not publicly available due to ethical restrictions. They may be made available on reasonable request (e.g., for replicating procedures and results) by the corresponding author (H.C.L.) after consultation with the co-authors.

Conflict of interest

M.K.R. Svačina, A. Meißner, F. Schweitzer, A. Ladwig, A. Sprenger-Svačina, I. Klein, H. Wüstenberg, C. Schneider, F. Kohle, N. B. Grether, G. Wunderlich, G.R. Fink, F. Klein and V. Di Cristanziano report no disclosures. H.C. Lehmann received honoraria for speaking and advisory board engagements or academic research support by Akcea, Alnylam, Biogen, Celgene, CSL Behring, Grifols, Gruenenthal, LFB Pharma, Takeda and UCB.

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Authors' contributions

MKRS designed and conceptualized the study, collected samples, analyzed and interpreted the data, and drafted and revised the manuscript for intellectual content. AM helped designing and conceptualizing the study, collected samples, analyzed and interpreted the data, and drafted and revised the manuscript for intellectual content. FS and AL supported study design, interpreted the data, and revised the manuscript for intellectual content. ASS, IK, HW, FKo, CS, NBG, GW, GRF and FK interpreted the data and revised the manuscript for intellectual content. VDC and HL designed and conceptualized the study, interpreted the data, and revised the manuscript for intellectual content.

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The authors thank all participating patients with immune neuropathies and all healthy subjects for study participation.

Figures and Table

Figure 1

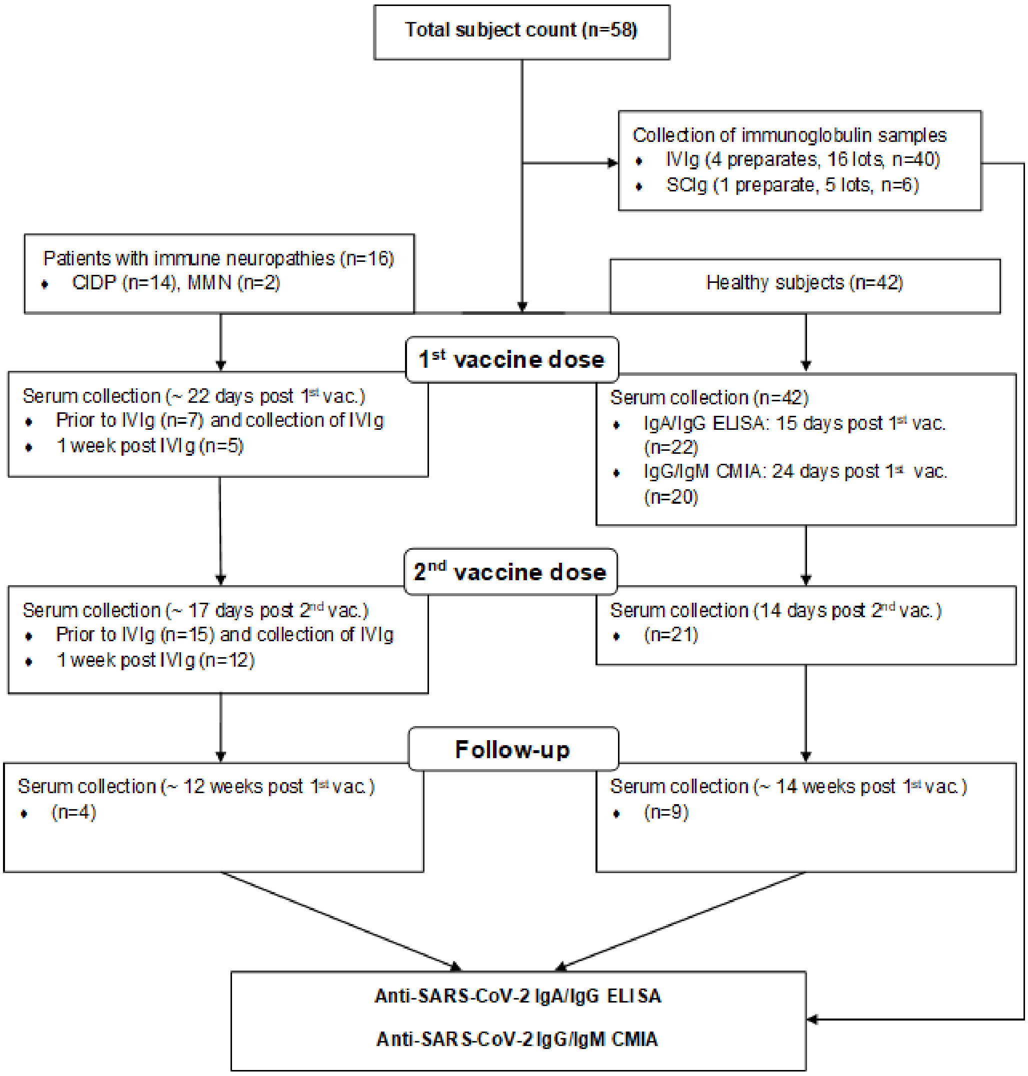

Figure 1 Flow chart of study conduction. ~ = *mean value*, *vac. = COVID-19 vaccine dose.*

Figure 2

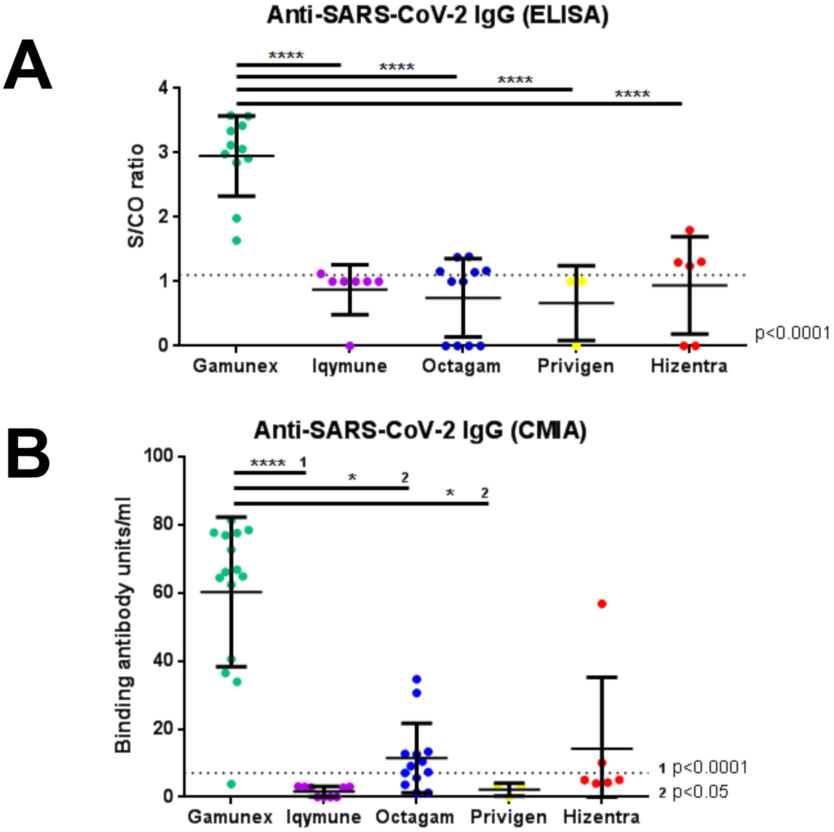

Figure 2 Analysis of anti-SARS-CoV-2 IgG titers within different immunoglobulin preparations.

S/CO ratio for anti-SARS-CoV-2 IgG was significantly higher for Gamunex® than for other therapeutic immunoglobulin preparations when performing anti-SARS-CoV-2 IgG ELISA ($p<0.0001$; **A**). Performing CMIA, Gamunex® showed significantly higher anti-SARS-CoV-2 IgG titers than other IVIg, but not compared to Hizentra® ($p<0.0001$, $p<0.05$; **B**). Both methods revealed that Gamunex®, Octagam® and Hizentra® were the most likely to contain anti-SARS-CoV-2 IgG whereas Iqymune® and Privigen® did not contain significant amounts of anti-SARS-CoV-2 IgG (**A** and **B**). (* $p<0.05$, ** $p<0.01$, *** $p<0.001$, **** $p<0.0001$). *S/CO ratio = sample-to-calibrator ratio, scattered bar = cut-off for positivity.*

Figure 3

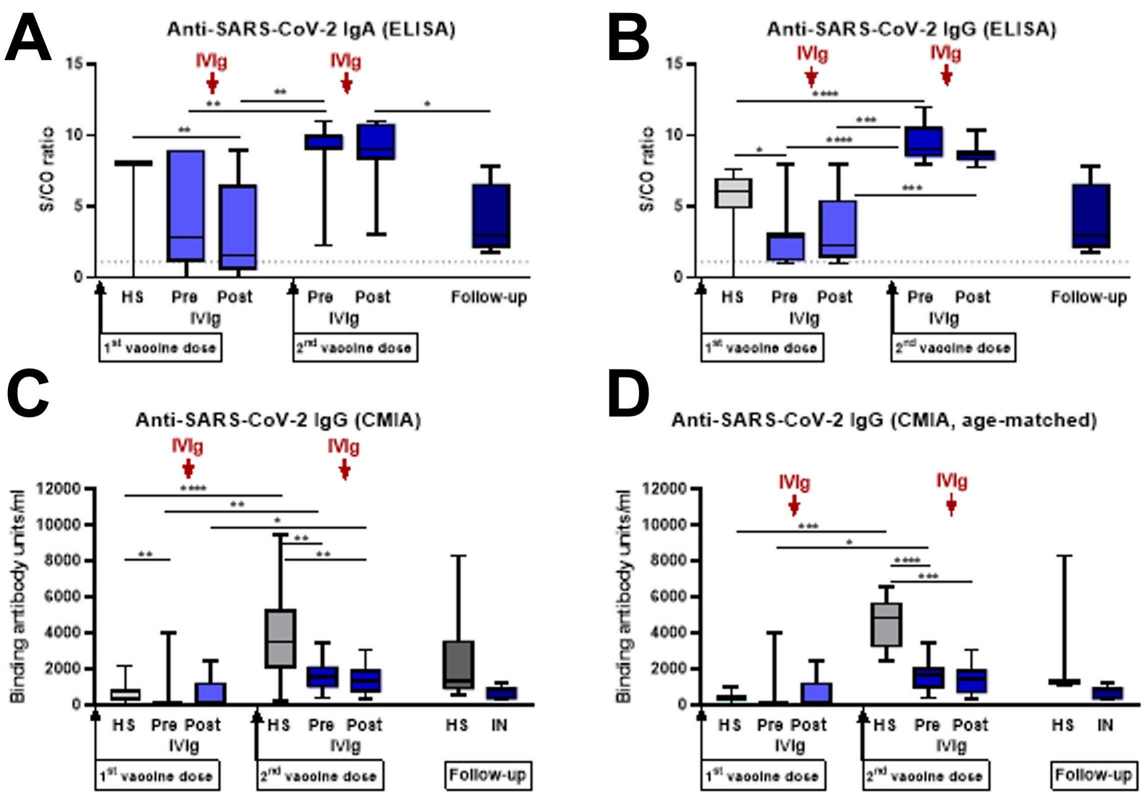

Figure 3 Serum titers of anti-SARS-CoV-2 antibodies. Anti-SARS-CoV-2 IgA shows a transient increase peaking after the 2^{nd} vaccine dose, anti-SARS-CoV-2 IgG shows a more sustained increase (**A-D**). IVIg does not significantly reduce anti-SARS-CoV-2 IgG titers after COVID-19 vaccination (**B-D**). Immune neuropathy patients show lower titers of anti-SARS-CoV-2 IgG especially after the 2^{nd} vaccine dose than younger or age-matched healthy subjects, but not at follow-up (**B-D**). (* p<0.05, ** p<0.01, *** p<0.001, **** p<0.0001). *Subject count after age-matching in D: 1^{st} vaccine dose [healthy subjects vs. immune neuropathy patients]: 7 vs. 7; 2^{nd} vaccine dose: 10 vs.10; Follow-up: 3 vs. 4. Scattered bar = cut-off for positivity. HS = healthy subjects, IN = immune neuropathy patients.*

	1st vaccine dose		2nd vaccine dose			Follow-up
IgM	Pre IVIg	Post IVIg	HS	Pre IVIg	Post IVIg	IVIg
Positive (n=)	1	1	10	0	1	0
Negative (n=)	6	4	19	8	4	2
Positive (%)	14.3	20	34.5	0	20	0

Table 1 Anti-SARS-CoV-2 IgM titers in patients with immune neuropathies and healthy subjects.
More healthy subjects show anti-SARS-CoV-2 IgM after the 2nd vaccine dose compared to immune neuropathy patients. *HS = healthy subjects, BAU/ml = binding antibody units per milliliter.*

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