Received: 16 February 2022 | Accepted: 13 July 2022

DOI: 10.1111/ene.15508

european journal of neurology
the official journal of the european academy of neurology

ORIGINAL ARTICLE

Antibody response after COVID-19 vaccination in intravenous immunoglobulin-treated immune neuropathies

Martin K. R. Svačina[1] | Anika Meißner[1] | Finja Schweitzer[1] | Anne Ladwig[1] | Alina Sprenger-Svačina[1] | Ines Klein[1] | Hauke Wüstenberg[1] | Felix Kohle[1] | Christian Schneider[1] | Nicolai B. Grether[1] | Gilbert Wunderlich[1] | Gereon R. Fink[1,2] | Florian Klein[3,4] | Veronica Di Cristanziano[3] | Helmar C. Lehmann[1]

[1]Department of Neurology, Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany

[2]Cognitive Neuroscience, Research Center Jülich, Institute of Neuroscience and Medicine (INM-3), Jülich, Germany

[3]Institute of Virology, Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany

[4]German Center for Infection Research, partner site Bonn-Cologne, Cologne, Germany

Correspondence
Helmar C. Lehmann, Department of Neurology, Medical Faculty and University Hospital of Cologne, Kerpener Straße 62, D-50937 Köln, Germany.
Email: helmar.lehmann@uk-koeln.de

Abstract

Background and purpose: 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 were analyzed for anti-SARS-CoV-2 IgG using enzyme-linked immunosorbent assay and chemiluminescent microparticle immunoassay. Blood sera from 16 patients with immune neuropathies were prospectively analyzed for anti-SARS-CoV-2 IgA, IgG, and IgM before and 1 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 ($p = 0.02$), whereas IgG titers remained stable ($p = 0.2$). IVIg did not significantly reduce intraindividual 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 2 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.

KEYWORDS
antibodies, anti-SARS-CoV-2 IgG, COVID-19 vaccine, IVIg, vaccine interaction

Veronica Di Cristanziano and Helmar C. Lehmann contributed equally.

INTRODUCTION

The use of therapeutic immunoglobulin, either administered intravenously (intravenous immunoglobulin [IVIg]) or subcutaneously (subcutaneous immunoglobulin [SCIg]), is an established therapy for immune neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN) [1–4]. IVIg contains IgG from >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], which may lead to a diminished seroconversion rate as observed in vaccinations with live attenuated viruses [13]. Furthermore, IVIg promotes anti-inflammatory immune pathways, like, activation of inhibitory Fc gamma receptor II b on B cells [14–16], which might reduce vaccine-stimulated anti-SARS-CoV-2 antibody production.

To assess the efficacy and safety of a coadministration of IVIg and COVID-19 mRNA vaccine, we (i) evaluated IVIg-derived anti-SARS-CoV-2 IgG titers in 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 European Federation of Neurological Societies/Peripheral Nerve Society criteria [17]) on regular IVIg treatment (1 g/kg bodyweight every 4–5 weeks); exclusion criteria were acute systemic infections, intake of immunosuppressants (i.e., cyclophosphamide or azathioprine) or monoclonal antibodies (i.e. rituximab), and previous COVID-19 infection. All participants underwent regular SARS-CoV-2 polymerase chain reaction testing and had no clinical history of COVID-19.

Paired serum samples before and 1 week after immunoglobulin treatment were collected from $n = 7$ patients 22 ± 4 days after the first, and $n = 15$ 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 opinion, suggesting an interval of a minimum of 2 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 took place 12 weeks after the first dose of COVID-19 vaccine (Figure 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, who were vaccinated with a COVID-19 mRNA vaccine and provided serum samples at intervals comparable to the immune neuropathy patients. Blood samples were collected 15 days (for IgA and IgG enzyme-linked immunosorbent assay [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 (Figure 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 six SCIg samples (Gamunex, five lots; Iqymune, three lots; Privigen, two lots; Octagam, six lots; Hizentra, SCIg, five 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, 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 semiquantitative assessment of antibody titers. An 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 CMIA

CMIA provided by Abbott (SARS-CoV-2 IgG II Quant and SARS-CoV-2 IgM) on the Alinity i system (Abbott, Abbott Park, IL, USA) was performed for quantitative assessment of anti-SARS-CoV-2

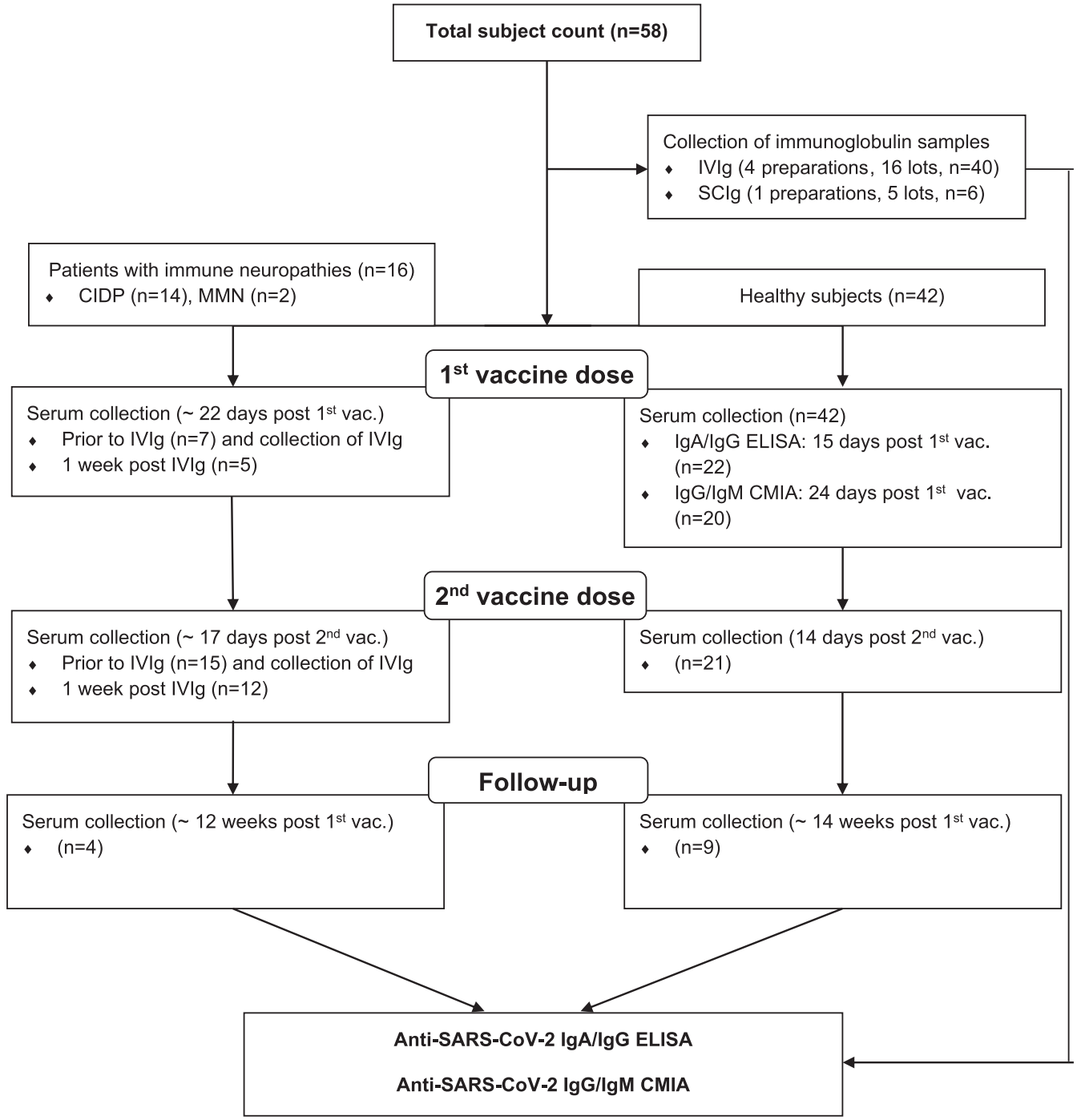

FIGURE 1 Flowchart of study conduction. ~, mean value; CIDP, chronic inflammatory demyelinating polyneuropathy; CMIA, chemiluminescent microparticle immunoassay; ELISA, enzyme-linked immunosorbent assay; IVIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy; SCIg, subcutaneous immunoglobulin; vac., COVID-19 vaccine dose

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 binding antibody units (BAU)/ml 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. An 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 SD 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 analysis of variance followed by Dunn 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), which was 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, five lots; Iqymune, three lots; Privigen, two lots; Octagam, six lots) and six SCIg samples (Hizentra, five lots) collected between March and July 2021, 24 of 46 samples (52%, CMIA), and 21 of 38 samples (55%, ELISA) showed relevant IgG reactivity against SARS-CoV-2 (Figure 2a,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 of 46 samples.

Anti-SARS-CoV-2 IgG titers were significantly higher in Gamunex than in other immunoglobulin preparations in both assays ($p < 0.0001$; Figure 2a,b). Five of 11 (ELISA) or eight of 13 (CMIA) Octagam samples, and four of six (ELISA) or two of six (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 (Figure 2a,b).

Anti-SARS-CoV-2 IgG titers varied between immunoglobulin brands and lots and even within the same lot, that is, 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, $p = 0.09$; Figure 3a). 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 ($p = 0.45$; Figure 3a). 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 ($p = 0.02$; Figure 3a).

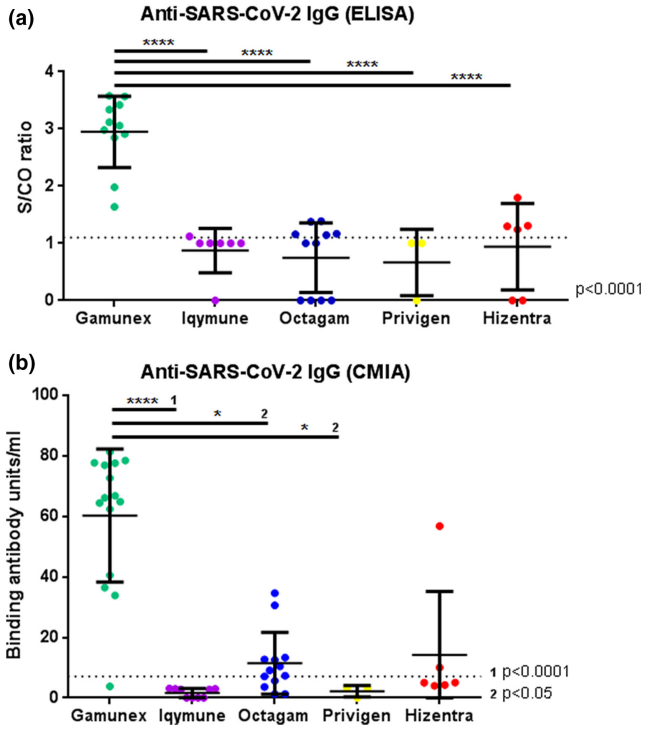

FIGURE 2 Analysis of anti-SARS-CoV-2 IgG titers within different immunoglobulin preparations. (a) Sample-to-calibrator ratio (S/CO ratio) for anti-SARS-CoV-2 IgG was significantly higher for Gamunex than for other therapeutic immunoglobulin preparations when performing anti-SARS-CoV-2 IgG enzyme-linked immunosorbent assay (ELISA; $p < 0.0001$). (b) In performing chemiluminescent microparticle immunoassay (CMIA), Gamunex showed significantly higher anti-SARS-CoV-2 IgG titers than other intravenous immunoglobulins, but not compared to Hizentra ($p < 0.0001$, $p < 0.05$). 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. $^{*}p < 0.05$, $^{****}p < 0.0001$. Dotted lines indicate cutoff for positivity

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, $p = 0.011$; Figure 3b). Like IgA antibody titers, anti-SARS-CoV-2 IgG titers significantly increased after the second vaccine dose and remained stable after 12 weeks ($p = 0.2$; Figure 3b).

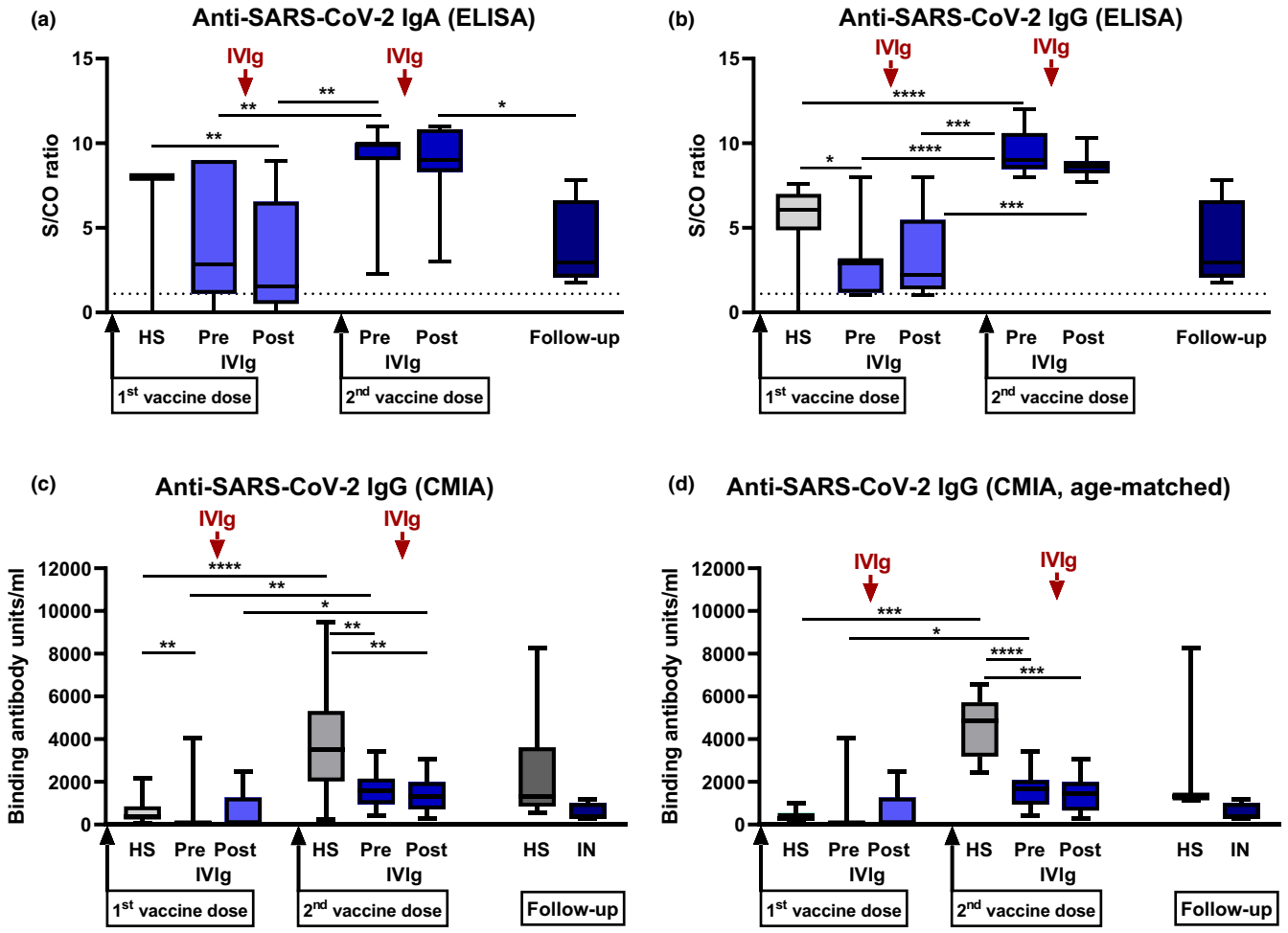

FIGURE 3 Serum titers of anti-SARS-CoV-2 antibodies. (a,b) Anti-SARS-CoV-2 IgA shows a transient increase peaking after the second vaccine dose, whereas anti-SARS-CoV-2 IgG shows a more sustained increase. (b–d) IVIg does not significantly reduce anti-SARS-CoV-2 IgG titers after COVID-19 vaccination. Immune neuropathy patients show lower titers of anti-SARS-CoV-2 IgG, especially after the second vaccine dose, than younger or age-matched healthy subjects, but not at follow-up. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$. (d) Subject count after age-matching: first vaccine dose (healthy subjects vs. immune neuropathy patients): 7 versus 7; second vaccine dose: 10 versus 10; follow-up: 3 versus 4. Dotted lines indicate cutoff for positivity. CMIA, chemiluminescent microparticle immunoassay; ELISA, enzyme-linked immunosorbent assay; HS, healthy subjects; IN, immune neuropathy patients; IVIg, intravenous immunoglobulin; S/CO ratio, sample-to-calibrator ratio

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 (Figure 3c,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 (immune neuropathy patients vs. healthy subjects: 615 ± 1509 BAU/ml vs. 627 ± 577 BAU/ml, $p = 0.71$; Figure 3c). 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, $p = 0.007$; Figure 3c). Also, anti-SARS-CoV-2 IgG titers were significantly lower in patients than in healthy subjects after the second vaccine dose ($p = 0.003$; Figure 3c). Age matching eliminated these intergroup differences after the first vaccine dose, whereas the difference persisted after the second vaccine dose ($p < 0.0001$) without being influenced by IVIg ($p = 0.69$; Figure 3d). 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 in follow-up anti-SARS-CoV-2 IgG titers compared to those after the second vaccine dose in both cohorts ($p = 0.07$; Figure 3c,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 nonsignificant decrease of serum anti-SARS-CoV-2 IgG titers in all patients with immune neuropathies (Figure 3b–d).

The percental serum anti-SARS-CoV-2 IgG titer decrease (1 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 coadministration 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 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. Because 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 2 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 at 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 versus 627 ± 577 [range = 50–2179] BAU/ml versus 615 ± 1509 [range = 10–4038] BAU/ml; after the second vaccine dose, 2595 [range = 1665–3089] BAU/ml versus 3776 ± 2376 [range = 228–9499] BAU/ml versus 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%

TABLE 1 Anti-SARS-CoV-2 IgM titers in patients with immune neuropathies and healthy subjects

	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

Note: More healthy subjects show anti-SARS-CoV-2 IgM after the second vaccine dose compared to immune neuropathy patients.

Abbreviations: HS, healthy subjects; IVIg, intravenous immunoglobulin.

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 cutoff 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 finding that none of the immune neuropathy patients developed COVID-19 until July 2021. To our knowledge, our study is the first that studied postvaccine 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 exposure [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 AstraZeneca 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 our study being 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 2 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.

AUTHOR CONTRIBUTIONS

Martin K. R. Svačina: Conceptualization (lead); data curation (lead); formal analysis (equal); investigation (lead); methodology (lead); project administration (lead); visualization (lead); writing – original draft (lead); writing – review and editing (lead). **Anika Meißner:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); supervision (supporting); validation (equal); visualization (supporting); writing – original draft (supporting); writing – review and editing (equal). **Finja Schweitzer:** Conceptualization (equal); data curation (supporting); formal analysis (equal); investigation (equal); methodology (equal); project administration (supporting); supervision (equal); validation (equal); visualization (equal); writing – original draft (supporting); writing – review and editing (equal). **Anne Ladwig:** Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (equal); supervision (equal); writing – review and editing (equal). **Alina Sprenger-Svačina:** Conceptualization (supporting); data curation (supporting); formal analysis (supporting); investigation (supporting); methodology (supporting); supervision (equal); validation (equal); writing – review and editing (equal). **Ines Klein:** Data curation (supporting); formal analysis (supporting); investigation (supporting); supervision (equal); validation (equal); writing – review and editing (equal). **Hauke Wüstenberg:** Formal analysis (supporting); investigation (supporting); methodology (supporting); validation (equal); writing – review and editing (equal). **Felix Kohle:** Investigation (supporting); methodology (supporting); supervision (equal); writing – review and editing (equal). **Christian Schneider:** Investigation (supporting); supervision (equal); validation (equal); writing – review and editing (equal). **Nicolai B. Grether:** Investigation (supporting); supervision (equal); validation (supporting); writing – review and editing (equal). **Gilbert Wunderlich:** Formal analysis (supporting); supervision (equal); validation (supporting); writing – review and editing (equal). **Gereon R. Fink:** Supervision (equal);

validation (equal); writing – review and editing (equal). **Florian Klein:** Formal analysis (equal); methodology (equal); supervision (lead); validation (equal); writing – review and editing (equal). **Veronica Di Cristanziano:** Conceptualization (equal); formal analysis (lead); investigation (lead); methodology (equal); project administration (equal); resources (lead); supervision (lead); validation (equal); visualization (supporting); writing – review and editing (lead). **Helmar C. Lehmann:** Conceptualization (lead); formal analysis (equal); investigation (equal); methodology (lead); project administration (equal); supervision (lead); validation (lead); visualization (equal); writing – original draft (equal); writing – review and editing (lead).

ACKNOWLEDGMENTS

The authors thank all participating patients with immune neuropathies and all healthy subjects for study participation. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

H.C.L. has received honoraria for speaking and advisory board engagements or academic research support from Akcea, Alnylam, Biogen, Celgene, CSL Behring, Grifols, Gruenenthal, LFB Pharma, Takeda, and UCB. None of the other authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

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.

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.

ORCID

Felix Kohle https://orcid.org/0000-0002-4429-0367
Helmar C. Lehmann https://orcid.org/0000-0001-6205-2293

REFERENCES

1. Oaklander AL, Lunn MPT, Hughes RA, van Schaik IN, Frost C, Chalk CH. Treatments for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): an overview of systematic reviews. *Cochrane Database Syst Rev*. 2017;2017:CD010369.
2. Van den Bergh PYK, Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society Guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint Task Force — Second Revision. *J Peripher Nerv Syst*. 2021;26(3):242-268.
3. van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (CIDP), a multicenter randomized double-blind placebo-controlled trial: the Path study. *J Neurol Sci*. 2017;381:59.
4. Markvardsen LH, Harbo T. Subcutaneous immunoglobulin treatment in CIDP and MMN. Efficacy, treatment satisfaction and costs. *J Neurol Sci*. 2017;378:19-25.
5. Lehmann HC, Hartung HP. Plasma exchange and intravenous immunoglobulins: mechanism of action in immune-mediated neuropathies. *J Neuroimmunol*. 2011;231:61-69.
6. Svačina MKR, Röth P, Bobylev I, et al. Changes of serum IgG dimer levels after treatment with IVIg in Guillain-Barré syndrome. *J Neuroimmune Pharmacol*. 2019;14:642-648.
7. Tremblay T, Paré I, Bazin R. Immunoglobulin G dimers and immune complexes are dispensable for the therapeutic efficacy of intravenous immune globulin in murine immune thrombocytopenia. *Transfusion*. 2013;53:261-269.
8. Ritter C, Bobylev I, Lehmann HC. Chronic inflammatory demyelinating polyneuropathy (CIDP): change of serum IgG dimer levels during treatment with intravenous immunoglobulins. *J Neuroinflammation*. 2015;12:148.
9. Dalakas MC, Bitzogli K, Alexopoulos H. Anti-SARS-CoV-2 antibodies within IVIg preparations: cross-reactivities with seasonal coronaviruses, natural autoimmunity, and therapeutic implications. *Front Immunol*. 2021;12:627285.
10. Kubota-Koketsu R, Terada Y, Yunoki M, et al. Neutralizing and binding activities against SARS-CoV-1/2, MERS-CoV, and human coronaviruses 229E and OC43 by normal human intravenous immunoglobulin derived from healthy donors in Japan. *Transfusion*. 2021;61:356-360.
11. Roy B, Litchman T, Torabi T, Nowak RJ. Influenza vaccination in autoimmune neuromuscular diseases: a survey of current practices and perceptions. *Muscle Nerve*. 2021;63:918-923.
12. Goldman RD, Yan TD, Seiler M, et al. Caregiver willingness to vaccinate their children against COVID-19: cross sectional survey. *Vaccine*. 2020;38:7668-7673.
13. Siber GR, Werner BG, Halsey NA, et al. Interference of immune globulin with measles and rubella immunization. *J Pediatr*. 1993;122:204-211.
14. Tackenberg B, Jelčić I, Baerenwaldt A, et al. Impaired inhibitory Fcγ receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. *Proc Natl Acad Sci USA*. 2009;106:4788-4792.
15. Ritter C, Förster D, Albrecht P, Hartung HP, Kieseier BC, Lehmann HC. IVIG regulates BAFF expression in patients with chronic inflammatory demyelinating polyneuropathy (CIDP). *J Neuroimmunol*. 2014;274:225-229.
16. Hartung HP. Advances in the understanding of the mechanism of action of IVIg. *J Neurol*. 2008;255:3-6.
17. Van Den Bergh PYK, Hadden RDM, Bouche P, et al. European federation of neurological societies/peripheral nerve society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripher. *Eur J Neurol*. 2010;17:356-363.
18. Doneddu PE, Spina E, Briani C, Fabrizi GM, Manganelli F, Nobile-Orazio E. Acute and chronic inflammatory neuropathies and COVID-19 vaccines: practical recommendations from the task force of the Italian Peripheral Nervous System Association (ASNP). *J Peripher Nerv Syst*. 2021;26:148-154.
19. Alhazzani W, Møller MH, Arabi YM, et al. Surviving sepsis campaign: guidelines on the management of critically Ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;48:E440-E469.
20. Harritshøj LH, Gybel-Brask M, Afzal S, et al. Comparison of 16 serological SARS-CoV-2 immunoassays in 16 clinical laboratories. *J Clin Microbiol*. 2021;59:e02596-20.
21. Narasimhan M, Mahimainathan L, Araj E, et al. Clinical evaluation of the Abbott alinity SARS-CoV-2 spike-specific quantitative IgG and IgM assays among infected, recovered, and vaccinated groups. *J Clin Microbiol*. 2021;59:e0038821.

22. Eberhardt KA, Dewald F, Heger E, et al. Evaluation of a New Spike (S)-protein-based commercial immunoassay for the detection of anti-SARS-CoV-2 IgG. *Microorg*. 2021;9:733.
23. Rychert J, Couturier MR, Elgort M, et al. Evaluation of 3 SARS-CoV-2 IgG antibody assays and correlation with neutralizing antibodies. *J Appl Lab Med*. 2021;6:614-624.
24. Balsby D, Nilsson AC, Möller S, et al. Determinants of antibody response to a third SARS-CoV-2 mRNA vaccine dose in solid organ transplant recipients: results from the prospective cohort study COVAC-Tx. *Vaccines (Basel)*. 2022;10:565.
25. Serra A, Marzo N, Pons B, Maduell P, López M, Grancha S. Characterization of antibodies in human immunoglobulin products from different regions worldwide. *Int J Infect Dis*. 2021;104:610-616.
26. Boban M. Novel coronavirus disease (COVID-19) update on epidemiology, pathogenicity, clinical course and treatments. *Int J Clin Pract*. 2021;75:e13868.
27. Furer V, Eviatar T, Zisman D, et al. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study.
28. Shapira G, Abu Hamad R, Weiner C, et al. Population differences in antibody response to SARS-CoV-2 infection and BNT162b2 vaccination. *FASEB J*. 2022;36:e22223.
29. Sahin U, Muik A, Vogler I, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. *Nat Res*. 2021;595:572-577.
30. Oberhardt V, Luxenburger H, Kemming J, et al. Rapid and stable mobilization of CD8+ T cells by SARS-CoV-2 mRNA vaccine. *Nature*. 2021;597:268-273.
31. Sterlin D, Mathian A, Miyara M, et al. IgA dominates the early neutralizing antibody response to SARS-CoV-2. *Sci Transl Med*. 2021;13:eabd2223.
32. Beavis KG, Matushek SM, Abeleda APF, et al. Evaluation of the EUROIMMUN anti-SARS-CoV-2 ELISA assay for detection of IgA and IgG antibodies. *J Clin Virol*. 2020;129:104468.
33. Lesny P, Anderson M, Cloherty G, et al. Immunogenicity of a first dose of mRNA- or vector-based SARS-CoV-2 vaccination in dialysis patients: a multicenter prospective observational pilot study. *J Nephrol*. 2021;34:975-983.
34. Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. *Open Forum Infect Dis*. 2020;7:1-6.
35. Hu B, Huang S, Yin L. The cytokine storm and COVID-19. *J Med Virol*. 2021;93:250-256.
36. Rojas M, Rodríguez Y, Monsalve DM, et al. Convalescent plasma in Covid-19: possible mechanisms of action. *Autoimmun Rev*. 2020;19:102554.
37. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically Ill patients with COVID-19 with convalescent plasma. *JAMA*. 2020;323:1582-1589.
38. Jawhara S. Could intravenous immunoglobulin collected from recovered coronavirus patients protect against covid-19 and strengthen the immune system of new patients? *Int J Mol Sci*. 2020;21:2272.

How to cite this article: Svačina MKR, Meißner A, Schweitzer F, et al. Antibody response after COVID-19 vaccination in intravenous immunoglobulin-treated immune neuropathies. *Eur J Neurol*. 2022;00:1-9. doi: 10.1111/ene.15508

MANAGE-PD

Tool for Making Informed Decisions to **Aid Timely Management of Parkinson's Disease**

MANAGE-PD allows you to:

- Identify PD patients inadequately controlled on oral medications
- Determine which patients with PD may be adequately controlled on their current treatment regimen or may require changes to their treatment regimen

Scan the QR code to access to the web

Click here to access to the web

MANAGE-PD is an AbbVie Inc. registered Medical Device. It is a collaborative research and development effort between AbbVie Medical Affairs and Health Economics and Outcomes, the Parkinson's Foundation and an international panel of Movement Disorder Specialists.

PD: Parkinson´s Disease

Parkinson's Foundation

Veeva Code: ABBV-AA-00335-FM Approved: January 2022

abbvie