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ORIGINAL ARTICLE

Immunomodulatory effects of intravenous and subcutaneous immunoglobulin in chronic inflammatory demyelinating polyneuropathy: An observational study

Martin K. R. Svačina[1] | Anika Meißner[1] | Finja Schweitzer[1] | Anne Ladwig[1] | Kalliopi Pitarokoili[2] | David M. Kofler[3] | Alina Sprenger-Svačina[1] | Christian Schneider[1,4] | Felix Kohle[1] | Ines Klein[1] | Hauke Wüstenberg[1] | Helmar C. Lehmann[1,5]

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

[2]Department of Neurology, St. Josef Hospital, Ruhr-University Bochum, Bochum, Germany

[3]Medical Clinic I, Department of Immunology and Rheumatology, Faculty of Medicine, University Hospital of Cologne, Cologne, Germany

[4]Department of Neurology, St. Katharinen Hospital, Frechen, Germany

[5]Department of Neurology, Clinic of Leverkusen gGmbH, Leverkusen, Germany

Correspondence
Martin K. R. Svačina, Department of Neurology, McGovern Medical School at UTHealth Science Center Houston, 6431 Fannin Street, Houston, TX 77030, USA.
Email: martin.k.svacina@uth.tmc.edu and martin.svacina@uk-koeln.de

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Abstract

Background and purpose: It is not known whether the route of administration affects the mechanisms of action of therapeutic immunoglobulin in chronic inflammatory demyelinating polyneuropathy (CIDP). The aim of this study, therefore, was to compare the immunomodulatory effects of intravenous (IVIg) and subcutaneous immunoglobulin (SCIg) in patients with CIDP and in IVIg-treated common variable immunodeficiency (CVID) patients.

Methods: Serum and peripheral blood mononuclear cell samples were obtained from 30 CIDP patients receiving IVIg, 10 CIDP patients receiving SCIg, and 15 patients with CVID receiving IVIg. Samples and clinical data were obtained prior to IVIg/SCIg and at 3 days, 7 days, and, in CIDP patients receiving IVIg, 21 days post-administration. Serum cytokines were assessed by Luminex-based multiplex assay and enzyme-linked immunosorbent assay. Immune cells were characterized by flow cytometry.

Results: Immune cell profiles of CIDP and CVID patients differed in frequencies of myeloid dendritic cells and cytotoxic natural killer cells. During treatment with IVIg or SCIg in CIDP patients, cellular immunomarkers were largely similar. CIDP patients receiving IVIg had higher macrophage inflammatory protein (MIP)-1α ($p=0.01$), interleukin (IL)-4 ($p=0.04$), and IL-33 ($p=0.04$) levels than SCIg recipients. IVIg treatment more broadly modulated cytokines in CIDP than SCIg treatment.

Conclusions: Our study demonstrates that the modulation of cellular immunomarkers in CIDP is independent of the application route of therapeutic immunoglobulin. Minor differences were observed between CIDP and CVID patients. In contrast, cytokines were differentially modulated by IVIg and SCIg in CIDP.

KEYWORDS
chronic inflammatory demyelinating polyneuropathy, cytokines, FcγRIIb/CD32b, immune cells, IVIg/SCIg

Martin K. R. Svačina and Anika Meißner contributed equally.

INTRODUCTION

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated disease associated with inflammatory demyelination of peripheral nerves and axonal damage [1, 2]. Plasma cell activation [3], pathogenic autoantibodies and complement activation [2, 4], resulting in macrophage-associated peripheral nerve damage [5, 6], are pathogenetic features.

Intravenous (IVIg) and subcutaneous immunoglobulin (SCIg) are pooled immunoglobulin G (IgG) solutions from more than 1000 healthy donors and are first-line therapies for CIDP [7]. In common variable immunodeficiency (CVID), IVIg or SCIg are used to substitute serum IgG [8, 9].

In CIDP, IVIg exerts various immunomodulatory effects, such as: (I) anti-idiotypic binding of pathogenic autoantibodies [10, 11]; (II) modulation of inflammatory cytokines and complement [12–14]; (III) modulation of IgG recycling via neonatal Fc receptors [15]; and (IV) modulation of immune cells, especially by stimulating inhibitory Fc-gamma receptor IIb (FcγRIIb, CD32b) on B cells and monocytes [16, 17]. This latter effect is important in CIDP since impaired B-cell maturation and reduced CD32b expression on B cells and monocytes are IVIg-responsive features [17]. Furthermore, IVIg treatment reduces myeloid dendritic cells and cytotoxic natural killer cells (NK^{dim}) that are also involved in the pathogenesis of CIDP [18, 19].

Weekly SCIg self-administration is efficacious in CIDP and leads to more stable average serum IgG concentrations compared to monthly IVIg administration [20, 21]. However, the PATH study revealed that 19%–33% of CIDP patients that had initially shown good response to IVIg relapsed after switching from IVIg to SCIg therapy [22]. The fact that 70% of these relapsing patients ameliorated after the re-initiation of IVIg raises the question of whether IVIg and SCIg might differentially exert immunomodulatory effects in CIDP. Therefore, our study compared cellular and soluble immunomarkers of CIDP during IVIg or SCIg treatment. These changes were compared to the effects of IVIg in CVID.

METHODS

Study protocol and patients

A total of 40 patients with immunoglobulin-responsive CIDP were recruited at the Department of Neurology of the University Hospital of Cologne between January and April 2021. Thirty patients received recurrent IVIg treatment (1 g/kg body weight every 4 weeks for at least 3 months at study inclusion). Ten CIDP patients received recurrent SCIg treatment in a weekly dose of 0.4 g/kg body weight for at least 1 month at study inclusion. A cohort of 15 CVID patients on recurrent IVIg treatment (1 g/kg body weight for at least 3 months at study inclusion) served as a control group and was recruited at the local Department of Immunology and Rheumatology between March and April 2021.

Inclusion criteria were probable or confirmed CIDP according to the 2010 European Federation of Neurological Societies/Peripheral Nerve Society criteria [23], as well as confirmed CVID according to the 2019 European Society for Immunodeficiencies (ESID) Registry working definitions for the clinical diagnosis of CVID [24], and recurrent IVIg or SCIg treatment. The intake of immunosuppressants, systemic corticosteroids, monoclonal antibodies, and vaccinations, all within the previous 3 months, as well as a concomitant autoimmune disease, were exclusion criteria. All CIDP patients were seronegative for paranodal autoantibodies.

Blood serum and peripheral blood mononuclear cell samples were collected on the same day prior to IVIg or SCIg administration (0 days, baseline), and at 3 days (for CIDP patients), 7 days (for all cohorts), and 21 days (for CIDP patients receiving IVIg) follow-up (Figure 1). Disability was repeatedly assessed in all CIDP patients via the Inflammatory Neuropathy Cause and Treatment (INCAT) disability scale, the Medical Research Council (MRC) sum score, and the Inflammatory Rasch-built Overall Disability Scale (I-RODS; Figure 1).

Serum and peripheral blood mononuclear cell collection

Serum was isolated from whole blood via centrifugation and S-monovette® tubes with separator gel (Sarstedt) and stored at −20°C for further use. Peripheral blood mononuclear cells were isolated from whole blood collected in BD Vacutainer CPT™ tubes (BD Biosciences) and stored at −80°C for further use.

Flow cytometry

Cells were stained using anti-CD3 (OKT3)-BV650, anti-CD11c (3.9)-BV510, anti-CD14 (63D3)-PE, anti-CD16 (3G8)-APC/Cy7, anti-CD19 (HIB19)-PE/Cy7, anti-CD27 (O323)-BV785, anti-CD32b/c (S18005H)-APC, anti-CD56 (5.1H11)-PE Dazzle 594 antibodies (all from Biolegend), and anti-CD32a (#2)-FITC antibody (Sino Biological). CD32c shares an identical extracellular domain with CD32b and is expressed on monocytes and NK cells, but not B cells of individuals who carry the *FCGR2C-ORF* genotype (18% of the general population [25, 26]). Therefore, we assume that this antibody selectively stained inhibitory CD32b on B cells but might have co-stained activating CD32c on monocytes in a minority of individuals in our study. Flow cytometry data were acquired on an LSR Fortessa™ flow cytometer (BD Biosciences) and analyzed using FlowJo v.10.8.0 software (BD Biosciences). Forward scatter-A and forward scatter-H were used to exclude doublet cells. Forward and side scatter were used to gate the whole lymphocyte and monocyte populations. For the characterization of monocytes, CD3- and CD19-positive cells were excluded. Monocytes were defined as classical ($CD14^{+}CD16^{-}$), intermediate ($CD14^{+}CD16^{+}$), and non-classical ($CD14^{dim}CD16^{+}$) monocytes, either expressing activating CD32a or inhibitory CD32b receptors. CD32a and CD32b expression was analyzed on distinctive

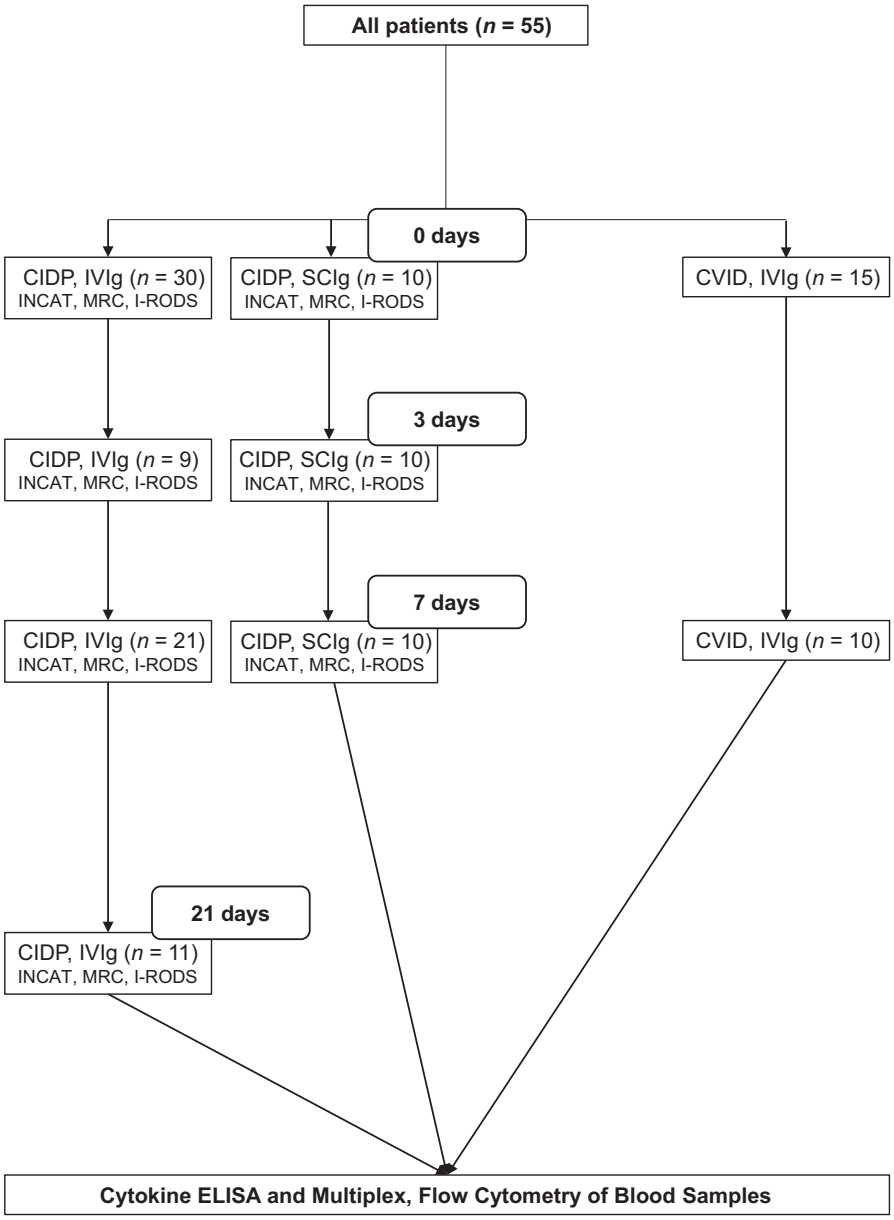

FIGURE 1 Flowchart of study conduction. Peripheral blood mononuclear cell samples were collected before and 3, 7 and 21 days after immunoglobulin administration for flow cytometry. Cytokine enzyme-linked immunosorbent assay (ELISA) and Luminex-based multiplex assay were performed with blood serum before and 3 and 7 days after immunoglobulin administration. In patients with chronic inflammatory demyelinating polyneuropathy (CIDP), Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, Medical Research Council (MRC) sum score and Rasch-built Overall Disability Scale (I-RODS) score were obtained. IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.

lymphocyte populations: $CD3^+CD32a^+$ and $CD3^+CD32b/c^+$ T cells, naïve $CD19^+CD27^-CD32a^+$ and $CD19^+CD27^-CD32b^+$ B cells, or memory $CD19^+CD27^+CD32a^+$ and $CD19^+CD27^+CD32b^+$ B cells. NK cells were characterized as cytotoxic NK^{dim} and cytokine-producing NK^{bright} cells via CD16 and CD56 expression ($CD16^+CD56^{dim}$, $CD16^+CD56^{bright}$). Myeloid dendritic cells were defined as $CD11c^+$ live cells that were negative for CD3, CD14, CD19 and CD56 (Figure S1). Whole cell counts were referred to their individual parental populations to assess percentual frequencies of all cell populations.

Luminex-based cytokine multiplex assay and transforming growth factor-β enzyme-linked immunosorbent assay

Serum concentrations of hepatocyte growth factor (HGF), interleukin (IL)-4, IL-10, IL-33, macrophage inflammatory protein (MIP)-1α, and MIP-1β were analyzed using a Luminex-based cytokine multiplex assay (Invitrogen ProcartaPlex, Thermo Fisher) on a Luminex-200 reader (Luminex) according to the manufacturers' instructions. Transforming growth factor (TGF)-β serum concentrations were analyzed via enzyme-linked immunosorbent assay (ELISA), using an Invitrogen TGF-β sandwich ELISA (Thermo Fisher) according to the manufacturer's instructions. Optical densities were measured at 450 nm, using BMG Labtech MARS® software (BMG Labtech).

Statistical analysis

GraphPad PRISM 9.0 software (GraphPad) was used for statistical analyses. Categorical variables were calculated as percentages or frequency distributions. Continuous variables were calculated as mean with standard deviation and range. D'Agostino and Pearson

omnibus normality tests were used to test for Gaussian distribution of values. Paired *t*-tests or Wilcoxon tests were used to compare paired values between two groups. For multiple comparisons of unpaired samples, one-way analysis of variance or Kruskal–Wallis tests with Bonferroni–Holm post hoc tests were performed. A p value <0.05 was taken to indicate statistical significance. Correlation analyses were performed using GraphPad PRISM or MATLAB version 9.10.0 (MathWorks). Pearson or Spearman correlation coefficients were calculated and displayed after using a modularity cluster analysis to identify similarly expressed cytokines.

Ethics approval and consent to participate

This study was conducted in accordance with the local laws at the University Hospital of Cologne, conformed with World Medical Association Declaration of Helsinki, and was registered in the German clinical trial register (DRKS00025759). Ethics approval was obtained from the Ethics Committee at the University of Cologne (approval reference number: 19-1662_1). All patients gave written informed consent for study participation.

RESULTS

Patients and clinical outcomes

Of 30 CIDP patients receiving IVIg, nine completed 3 days, 21 completed 7 days, and 11 completed 21 days of follow-up (Figure 1). This drop-out rate was derived from a COVID-19 high-incidence period before broad implementation of COVID-19 vaccines in Germany parallel to study conduction, therefore, several patients wished to reduce hospital appointments and were lost to follow-up. All SCIg recipients completed 3-day and 7-day follow-ups.

The mean age and gender ratios were not significantly different between the cohorts ($p = 0.09$; Table 1).

No significant difference was observed regarding disability between the CIDP cohorts (Table 1). In CIDP patients receiving IVIg, INCAT score and MRC sum score remained stable 21 days after IVIg administration. A non-significant tendency of clinical improvement was observed in I-RODS score ($p = 0.07$; Table 1).

Cellular immunomarkers in IVIg- and SCIg-treated CIDP

We first analyzed baseline cellular parameters in IVIg- or SCIg-treated CIDP, and IVIg-treated CVID patients. Subsequently, differences in cellular immunomarkers during IVIg and SCIg treatment were compared. For better readability, only differences that are relevant to the immunopathogenesis of CIDP are described (see also Table 2).

TABLE 1 Clinical characteristics of the patient cohorts.

Group	Gender ratio, male: female	Age, years	INCAT disability score				MRC sum score				I-RODS score, centile			
			Day 0	3	7	21	0	3	7	21	0	3	7	21
CIDP, IVIg	22:8	61 ± 15	2 ± 2	2 ± 2	2 ± 2	2 ± 1	57 ± 3	58 ± 2	57 ± 3	58 ± 3	66 ± 18	73 ± 16	69 ± 18	77 ± 15
CIDP, SCIg	7:3	62 ± 9	4 ± 3	5 ± 3	4 ± 3		52 ± 8	52 ± 7	53 ± 6		54 ± 24	54 ± 24	54 ± 24	
CVID, IVIg	10:5	50 ± 15												

Note: The gender ratios and mean age were comparable in CIDP patients. Patients with CVID tended to be younger, albeit not statistically significant ($p = 0.09$). INCAT score, MRC sum score and I-RODS score were stable prior to and after immunoglobulin treatment in both CIDP cohorts.

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CVID, common variable immunodeficiency; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Rasch-built Overall Disability Scale; IVIg, intravenous immunoglobulin; MRC, Medical Research Council; SCIg, subcutaneous immunoglobulin.

At baseline, reduced CD32a$^+$ classical (CD14$^+$CD16$^-$CD32a$^+$) monocytes in SCIg-treated CIDP patients compared to IVIg-treated CIDP patients could be observed, as well as reduced NK^{dim} cells in patients with CVID (Table 2).

Next, we analyzed differences in cellular immunomarkers by longitudinally comparing IVIg and SCIg treatment. No significant differences were observed at any of the time points between CIDP and CVID patients after IVIg or SCIg administration in the frequencies of total, naïve and memory B cells, T cells, and classical monocytes (Table 2). Frequencies of intermediate and non-classical monocytes, their referring CD32a$^+$ and/or CD32b/c$^+$ subtypes (all $p > 0.2$), and whole NK cells ($p = 0.8$) were not different between the cohorts.

CD32b$^+$ memory (CD19$^+$CD27$^+$CD32b$^+$) B cells decreased 7 days after IVIg or SCIg administration (Figure 2a) and then increased significantly compared to baseline after 21 days in IVIg-treated CIDP patients. CD32b$^+$ memory B-cell frequencies correlated with I-RODS score in IVIg-treated CIDP patients, but not in SCIg recipients ($r = 0.35$, $p = 0.007$). CD32b$^+$ naïve (CD19$^+$CD27$^-$CD32b$^+$) B cells transiently decreased after IVIg/SCIg treatment, before returning to baseline 21 days after IVIg treatment (Figure 2b, Table 2). Frequencies of CD32a$^+$ classical (CD14$^+$CD16$^-$CD32a$^+$) monocytes transiently increased 3 days after SCIg treatment, before significantly decreasing at day 7 in both CIDP cohorts, and again increasing 21 days post IVIg (Figure 2c, Table 2). CD32b/c$^+$ classical (CD14$^+$CD16$^-$CD32b/c$^+$) monocytes increased 7 days post IVIg in some CIDP patients, while others showed lower frequencies. Therefore, uniquely, a significant decrease was observed in SCIg recipients (Figure 2d, Table 2). Twenty-one days after IVIg treatment, frequencies of CD32b/c$^+$ classical (CD14$^+$CD16$^-$CD32b/c$^+$) monocytes were comparable to baseline. Myeloid dendritic cells were increased 7 days after IVIg and SCIg treatment in CIDP patients but decreased in IVIg-treated CVID patients (Figure 2e, Table 2). Cytotoxic (CD16$^+$CD56^{dim}) NK^{dim} cell frequencies decreased 7 days after IVIg/SCIg treatment in CIDP patients, but not in CVID patients, before returning to baseline values at day 21 (Figure 2f, Table 2). NK-^{bright} cells were not different between the cohorts ($p = 0.2$). Finally, a stronger increase in CD32a$^+$ naïve (CD19$^+$CD27$^-$CD32a$^+$) B cells in CVID compared to IVIg-treated CIDP patients could be observed (CVID vs. CIDP: 28 ± 22% vs. 10 ± 6%; $p = 0.008$).

To exclude a selection bias due to a high drop-out rate of the IVIg-receiving CIDP patients, a subgroup analysis of immune cell patterns, excluding all patients who only provided blood samples at baseline, was performed. Apart from significantly reduced myeloid dendritic cell frequencies (0.006 ± 0.003% vs. 14 ± 18%; $p = 0.04$) 21 days after IVIg treatment in CIDP patients, no relevant differences were observed compared to the initial analysis.

Cytokines are differentially modulated by IVIg and SCIg in CIDP

At baseline, CIDP patients harbored higher MIP-1α serum levels than CVID patients. MIP-1α levels transiently increased after IVIg, but not after SCIg administration in CIDP (Table 3, Figure 3a). IVIg-treated CIDP patients showed increased IL-4 and IL-33 serum levels compared to SCIg-treated CIDP patients (Table 3, Figure 3b). CVID patients had higher baseline TGF-β serum levels than IVIg-treated CIDP patients; this effect disappeared after IVIg administration (Table 3). No differences in serum levels of HGF ($p = 0.97$), IL-10 ($p = 0.2$), or MIP-1β ($p = 0.6$) were found within 7 days after IVIg or SCIg administration.

Multiple correlation cluster analyses revealed that IVIg-treated CIDP patients had broader concordant cytokine modulation than SCIg recipients, which peaked 3 days after IVIg treatment (Figure 3c). This was significant for IL-4 and IL-33 ($r_s = 0.66$, $p = 0.007$), IL-4 and IL-10 ($r_s = 0.77$, $p = 0.0008$), IL-10 and IL-33 ($r_s = 0.57$, $p = 0.03$), and IL-33 and MIP-1α ($r_s = 0.91$, $p < 0.0001$), all showing a simultaneous increase 7 days after IVIg administration. In SCIg-treated patients, the significant simultaneous increase of IL-4 and IL-10 disappeared after 7 days ($p = 0.82$), and only an anti-proportionality of IL-4 and HGF ($r_s = -0.78$, $p = 0.02$), as well as a proportional increase of IL-33 and MIP-1α ($r_s = 0.95$, $p = 0.0003$), persisted (Figure 3c). IL-4 and IL-33 serum levels correlated with CD32b/c$^+$ classical monocytes in IVIg-treated CIDP patients, but not in SCIg recipients (Table S1).

DISCUSSION

Our data indicate that the effects of IVIg and SCIg on cellular immunomarkers of CIDP are comparable, whereas serum cytokines are more diversely modulated by IVIg than SCIg.

Our observation that CD32b$^+$ memory B cells increased 21 days after IVIg administration is in line with previous studies that demonstrated their increase 3 weeks after IVIg administration in CIDP patients clinically responding to therapy [17], subsequent to an initial decrease 7 days after infusion [18]. Consistent with the study by Tackenberg et al. [17], this cell type correlated with disability measured by the I-RODS score in our IVIg-treated CIDP patients, but not in SCIg-treated CIDP patients. Considering a by-trend higher disability in the SCIg cohort, secondary axonal damage and/or SCIg-related placebo effects [27], leading to ongoing SCIg treatment despite minimal benefit, are possible explanations. However, the fact that, besides a transient increase of CD32b$^+$ memory B cells 3 days after SCIg administration, no relevant differences in terms of CD32b$^+$ memory B cell frequencies were observed between CIDP patients who received IVIg and those who received SCIg indicates that IVIg or SCIg treatment does not differentially alter this cellular immunomarker. Other cellular immunomarkers of CIDP were also not differentially modulated by IVIg and SCIg: no relevant difference was seen in CD32b/c$^+$ classical monocytes, which were previously reported to increase in CIDP patients responding to IVIg [17]. Interestingly, their frequencies increased only in some CIDP patients 7 days after IVIg administration. One explanation could be that a subgroup of patients with sustained immunological remission confounded the results due to a subjective IVIg response and continued to receive IVIg, which is in line with a recent study which

TABLE 2 Overview of immune cell alterations after intravenous or subcutaneous immunoglobulin therapy in patients with chronic inflammatory demyelinating polyneuropathy and patients with common variable immunodeficiency.

Cell type	Surface markers	Time point	CIDP + IVIg	CIDP + SCIg	CVID + IVIg	*p* value[a]
B cells	$CD3^-CD19^+$	Baseline	11 ± 6%	10 ± 4%	15 ± 12%	>0.99
		3 days	7 ± 3%	8 ± 3%		>0.99
		7 days	**40 ± 14%**	36 ± 22%	36 ± 24%	>0.99
		21 days	9 ± 5%			
		***p* value**[b]	**<0.0001**	0.21	0.29	
Memory B cells	$CD3^-CD19^+CD27^+$	Baseline	23 ± 18%	13 ± 8%	16 ± 21%	>0.99
		3 days	25 ± 15%	32 ± 17%		>0.99
		7 days	3 ± 3%	2 ± 1%	13 ± 20%	>0.99
		21 days	41 ± 22%			
		***p* value**	0.9	>0.99	>0.99	
$CD32b^+$ memory B cells	$CD3^-CD19^+CD27^+CD32b^+$	Baseline	26 ± 16%	13 ± 7%	12 ± 13%	0.07
		3 days	23 ± 15%	29 ± 17%		>0.99
		7 days	4 ± 4%	**4 ± 3%**	2 ± 3%	0.53
		21 days	**37 ± 23%**			
		***p* value**	**0.02**	**0.004**	0.44	
Naïve B cells	$CD3^-CD19^+CD27^-$	Baseline	77 ± 17%	86 ± 8%	82 ± 20%	>0.99
		3 days	75 ± 16%	69 ± 17%		>0.99
		7 days	**92 ± 6%**	34 ± 21%	87 ± 21%	>0.99
		21 days	59 ± 22%			
		***p* value**	**0.03**	>0.99	>0.99	
$CD32b^+$ naïve B cells	$CD3^-CD19^+CD27^-CD32b^+$	Baseline	47 ± 18%	58 ± 7%	36 ± 24%	>0.99
		3 days	41 ± 23%	37 ± 11%		>0.99
		7 days	**19 ± 14%**	**15 ± 7%**	**12 ± 11%**	0.09
		21 days	34 ± 21%			
		***p* value**	**<0.001**	**0.002**	**0.004**	
T cells	$CD3^+CD19^-$	Baseline	51 ± 18%	48 ± 16%	39 ± 19%	>0.99
		3 days	65 ± 14%	63 ± 15%		>0.99
		7 days	**12 ± 12%**	19 ± 16%	20 ± 23%	>0.99
		21 days	61 ± 10%			
		***p* value**	**<0.0001**	0.6	>0.99	
Classical monocytes	$CD14^+CD16^-$	Baseline	46 ± 36%	17 ± 14%	40 ± 38%	>0.99
		3 days	72 ± 14%	70 ± 19%		>0.99
		7 days	60 ± 35%	41 ± 27%	48 ± 31%	>0.99
		21 days	83 ± 7%			
		***p* value**	>0.99	>0.99	>0.99	
$CD32a^+$ classical monocytes	$CD14^+CD16^-CD32a^+$	Baseline	30 ± 22%	8 ± 7%	33 ± 32%	**0.04**
		3 days	35 ± 15%	35 ± 15%		>0.99
		7 days	**15 ± 13%**	**4 ± 4%**	52 ± 30%	>0.99
		21 days	68 ± 9%			
		***p* value**	**0.05**	**0.004**	>0.99	
$CD32b/c^+$ classical monocytes	$CD14^+CD16^-CD32b^+$	Baseline	13 ± 14%	14 ± 11%	16 ± 15%	>0.99
		3 days	13 ± 9%	12 ± 10%		>0.99
		7 days	13 ± 10%	**5 ± 8%**	16 ± 16%	>0.99
		21 days	11 ± 6%			
		***p* value**	0.6	**0.01**	0.6	

TABLE 2 (Continued)

Cell type	Surface markers	Time point	CIDP + IVIg	CIDP + SCIg	CVID + IVIg	*p* value[a]
Myeloid dendritic cells	($CD3^-CD19^-CD14^-CD56^-$) $CD11c^+$	Baseline	15 ± 18%	14 ± 11%	10 ± 12%	>0.99
		3 days	**0.02 ± 0.04%**	**0.01 ± 0.02%**		>0.99
		7 days	30 ± 27%	8 ± 8%	**30 ± 33%**	>0.99
		21 days	0.006 ± 0.003%			
		***p* value**	**0.02**	**0.006**	**0.003**	
Cytotoxic (NK^{dim}) natural killer cells	($CD3^-CD19^-CD14^-$) $CD16^+CD56^{dim}$	Baseline	26 ± 15%	23 ± 6%	10 ± 7%	**<0.0001**
		3 days	40 ± 10%	40 ± 5%		>0.99
		7 days	**7 ± 9%**	**9 ± 9%**	4 ± 6%	0.36
		21 days	25 ± 10%			
		***p* value**	**0.0004**	**0.0006**	>0.99	

Note: A selection of the most relevant cell populations is shown.Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CVID, common variable immunodeficiency; IVIg, intravenous immunoglobulin; SCIg, subcutaneous immunoglobulin.

[a]Inter-group comparisons.

[b]Intra-group comparisons (significantly different cell frequencies vs. baseline and the referring *p* values are written in bold characters).

demonstrated that the placebo effect is a common challenge after long-term immunoglobulin treatment in CIDP [27]. Furthermore, the reduction of NK^{dim} cell frequencies after IVIg administration, also a marker for IVIg response [19], was not significantly different to that in SCIg recipients. Likewise, myeloid dendritic cells were not differentially altered by IVIg and SCIg in CIDP. Finally, $CD32a^+$ classical monocytes were similarly reduced in CIDP patients after IVIg and SCIg treatment. CD32a is an essential activating immunoglobulin receptor that promotes phagocytosis in autoimmune diseases such as rheumatoid arthritis or systemic lupus [28, 29], and its deletion, amongst other immunoglobulin receptors, was shown to protect from peripheral nerve inflammation in an animal model of CIDP [30]. Therefore, it can be assumed that the reduction of $CD32a^+$ phagocytic classical monocytes also plays a therapeutic role in CIDP. Whether the higher baseline frequencies and the increase of $CD32a^+$ classical monocytes 21 days after IVIg treatment are derived from a rebound phenomenon following decreasing IVIg serum levels, which are commonly observed 3 weeks after IVIg administration [31–33], can only be speculated. However, the observation by Dyer et al. that IVIg initially tends to influence effectors of the innate immune response such as myeloid dendritic cells or monocytes [18], which is likely to precede alterations in adaptive immune effectors [17], could generally explain why the decrease of these cells occurred earlier than the increase of $CD32b^+$ memory B cells. IVIg induced a stronger increase of myeloid dendritic cells and naïve $CD32a^+$ B cells in CVID than in CIDP patients. Whether this effect contributes to an ameliorated immune response in CVID, where a defect B-cell differentiation is a pathogenic feature [8], needs to be examined in future studies.

In our study, IVIg and SCIg differentially modulated serum cytokines in CIDP patients. The observation that the kinetics of serum cytokines such as IL-4, IL-33 and MIP-1α were more stable after SCIg than after IVIg infusion might be a consequence of a more continuous alteration of cytokine release. This could be derived from more stable serum IgG levels after SCIg treatment [20, 21], and might reflect the lower rate of flu-like symptoms or headache after SCIg observed in the PATH study [22] as these are associated with the release of pro-inflammatory cytokines [34, 35]. Pro-inflammatory MIP-1α was elevated 3 days after IVIg treatment compared to SCIg treatment in CIDP patients, and our correlation analyses revealed that IVIg treatment more broadly modulated cytokines than SCIg treatment, with a peak in this difference after 3 days, which is within the typical period of infusion-related adverse effects [34, 35]. Differential infusion-related peak IgG serum levels might explain our observation of a significant correlation between IL-4, IL-33 and $CD32b/c^+$ classical monocytes only in IVIg and not in SCIg recipients: Anthony et al. reported that sialylated Fc fractions within IVIg induce an IL-33 release by binding to DC-SIGN receptors on myeloid cells, promoting basophils to secrete IL-4, which increases inhibitory CD32b expression on monocytes/macrophages to alleviate autoimmunity [36]. Although studies reported that SCIg treatment induces higher average serum IgG concentrations than IVIg treatment [20–22], one study revealed that a serum IgG level increase of more than Δ 7.31 g/L within the 2-week period after IVIg treatment was associated with a favorable outcome in Guillain–Barré syndrome, suggesting a therapeutic benefit of higher IVIg-related peak serum IgG levels than those observed with SCIg (PATH study: Δ 4.1 ± 2.7 g/L [22]). Although IVIg and SCIg are equally efficient in CIDP [22], lower post-infusion peak serum IgG levels with consecutively less DC-SIGN-associated IL-33 and IL-4 release might explain why our SCIg cohort did not show a correlation between these cytokines and $CD32b/c^+$ monocytes. Additionally, immunoglobulin pretreatment and, in some patients, secondary axonal damage and/or a placebo effect, might pose confounders that could mask possible interactions between cytokines and immune cells in these patients. However, as immunoglobulin effects are manifold beyond the DC-SIGN pathway [7], and inter-cohort cellular and clinical parameters were comparable, we did not find evidence for any therapeutical

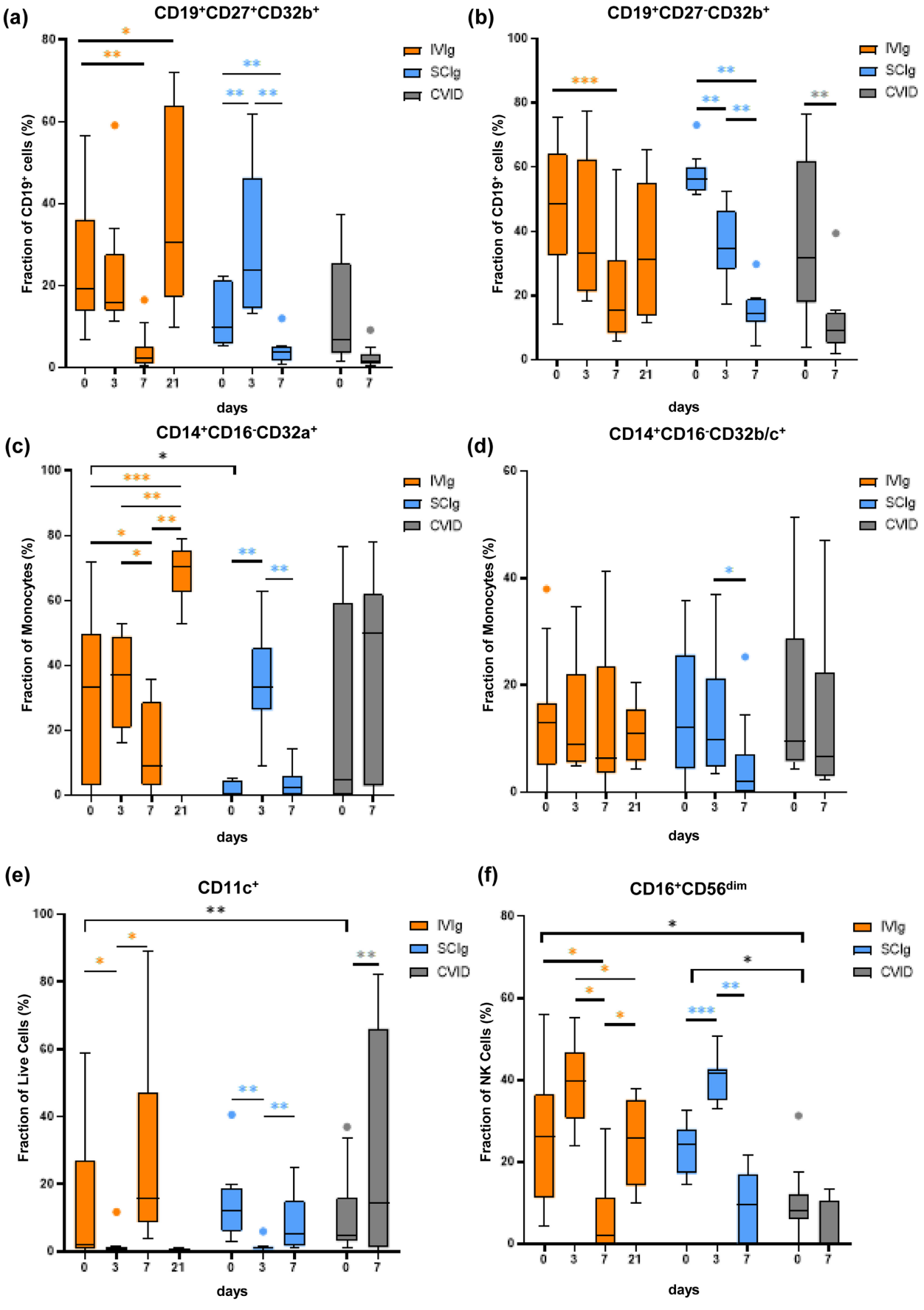
(a)
CD19+CD27+CD32b+
Fraction of CD19+ cells (%)
days
IVIg
SCIg
CVID
(b)
CD19+CD27-CD32b+
Fraction of CD19+ cells (%)
days
IVIg
SCIg
CVID
(c)
CD14+CD16-CD32a+
Fraction of Monocytes (%)
days
IVIg
SCIg
CVID
(d)
CD14+CD16-CD32b/c+
Fraction of Monocytes (%)
days
IVIg
SCIg
CVID
(e)
CD11c+
Fraction of Live Cells (%)
days
IVIg
SCIg
CVID
(f)
CD16+CD56dim
Fraction of NK Cells (%)
days
IVIg
SCIg
CVID

FIGURE 2 Cellular immunomarkers before and after administration of intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin (SCIg). The frequencies of CD32b-expressing memory B cells increased 21 days after IVIg infusion (a), whereas CD32b-expressing naïve B cells tended to decrease after IVIg/SCIg administration (b). IVIg and SCIg infusion decreased the frequencies of CD32a-expressing classical monocytes within 7 days post infusion (c), whereas CD32b/c-expressing monocytes mostly remained unaltered (d). common variable immunodeficiency (CVID) patients showed elevated frequencies of myeloid dendritic cells compared to chronic inflammatory demyelinating polyneuropathy (CIDP) patients, and IVIg reduced their frequencies in CIDP patients (e), NK^{dim} cell frequencies were significantly reduced 7 days after IVIg or SCIg administration in CIDP patients (f). $CD19^+CD27^+CD32b^+$, $CD32b^+$ memory B cells; $CD19^+CD27^-CD32b^+$, $CD32b^+$ naïve B cells; $CD14^+CD16^-CD32a^+$, $CD32a^+$ classical monocytes; $CD14^+CD16^-CD32b/c^+$, $CD32b/c^+$ classical monocytes; $CD11c^+$, myeloid dendritic cells; $CD16^+CD56^{dim}$, natural killer $(NK)^{dim}$ cells. $^*p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$.

TABLE 3 Overview of cytokine alterations after intravenous or subcutaneous immunoglobulin therapy in patients with chronic inflammatory demyelinating polyneuropathy and patients with common variable immunodeficiency.

Cytokine	Timepoint	CIDP + IVIg	CIDP + SCIg	CVID + IVIg	*p* value[a]
MIP-1α	Baseline	21 ± 26 pg/mL	26 ± 27 pg/mL	7 ± 3 pg/mL	**0.02**
	3 days	50 ± 31 pg/mL	29 ± 32 pg/mL		**0.04**
	7 days	**36 ± 26 pg/mL**	24 ± 27 pg/mL	13 ± 6 pg/mL	**0.01**
	***p* value**[b]	**0.03**	ns	ns	
IL-4	Baseline	46 ± 135 pg/mL	6 ± 8 pg/mL	12 ± 3 pg/mL	**0.03**
	3 days	81 ± 171 pg/mL	6 ± 7 pg/mL		**0.04**
	7 days	48 ± 123 pg/mL	5 ± 8 pg/mL	14 ± 4 pg/mL	**0.04**
	***p* value**[b]	ns	ns	ns	
IL-33	Baseline	82 ± 276 pg/mL	13 ± 24 pg/mL	2 ± 1 pg/mL	ns
	3 days	182 ± 402 pg/mL	15 ± 28 pg/mL		**0.03**
	7 days	94 ± 274 pg/mL	10 ± 21 pg/mL	5 ± 9 pg/mL	**0.04**
	***p* value**[b]	ns	ns	ns	
TGF-β	Baseline	25 ± 7 ng/mL	29 ± 8 ng/mL	36 ± 8 ng/mL	**0.04**
	3 days	21 ± 7 ng/mL	28 ± 7 ng/mL		ns
	7 days	25 ± 9 ng/mL	24 ± 5 ng/mL	30 ± 7 ng/mL	ns
	***p* value**[b]	ns	ns	ns	

Note: A selection of relevantly altered cytokines is shown. Abbreviation: CIDP, chronic inflammatory demyelinating polyneuropathy; CVID, common variable immunodeficiency; IVIg, intravenous immunoglobulin; IL, interleukin; SCIg, subcutaneous immunoglobulin; MIP, macrophage inflammatory protein; ns, nonsignificant; TGF-β, transforming growth factor-β.

[a]Inter-group comparisons.

[b]Intra-group comparisons (significantly different cytokine levels vs. baseline and the referring *p* values are written in bold characters).

relevance of the differential IL-4/IL-33/$CD32b/c^+$ findings between the CIDP cohorts. A correlation of IL-33 and MIP-1α persisted 7 days after IVIg or SCIg treatment in the two CIDP cohorts, which could generally suggest an immunomodulatory pathway. Whereas the anti-inflammatory potential of IL-33 in immune neuropathies has been described [37], it appears controversial that serum levels of MIP-1α positively correlated with this anti-inflammatory cytokine. MIP-1α is a macrophage-attracting factor that is increased in CIDP, and its nerve tissue levels correlated with neuroinflammation in experimental autoimmune neuritis [38, 39]. By contrast, an in vitro study demonstrated that the chemoattractive potential of MIP-1α is negligible compared to that of MIP-1β [40], and the fact that we investigated MIP-1α serum and not nerve tissue levels of CIDP patients leads to the assumption that serum MIP-1α might still mediate anti-inflammatory effects via a possible IL-33/MIP-1α pathway. Further studies are warranted to evaluate the relationship between MIP-1α serum levels and cellular immunomarkers such as CD32b-expressing memory B cells in untreated CIDP patients and after initial IVIg/SCIg treatment, as differential MIP-1α levels in our IVIg and SCIg cohorts did not differentially alter the immune cell composition in pre-treated and clinically stable CIDP patients, making a causal association uncertain. Furthermore, the overall differential cytokine modulation after IVIg or SCIg infusion did not impact the immune cell composition in CIDP.

One limitation of our study is the fact that immune cells were not examined 21 days after SCIg administration, which could limit the comparability to IVIg. However, as all SCIg recipients had repeatedly administered SCIg weekly for at least 1 month at study inclusion, it appears very likely that immune cell compositions 21 days after SCIg administration and at baseline would be similar, as this time point reflects the baseline of a subsequent SCIg cycle.

Another confounding factor is that approximately two-thirds of IVIg-receiving CIDP patients were lost to 3- and 21-day follow-ups due to their wish to reduce hospital appointments to a minimum, as

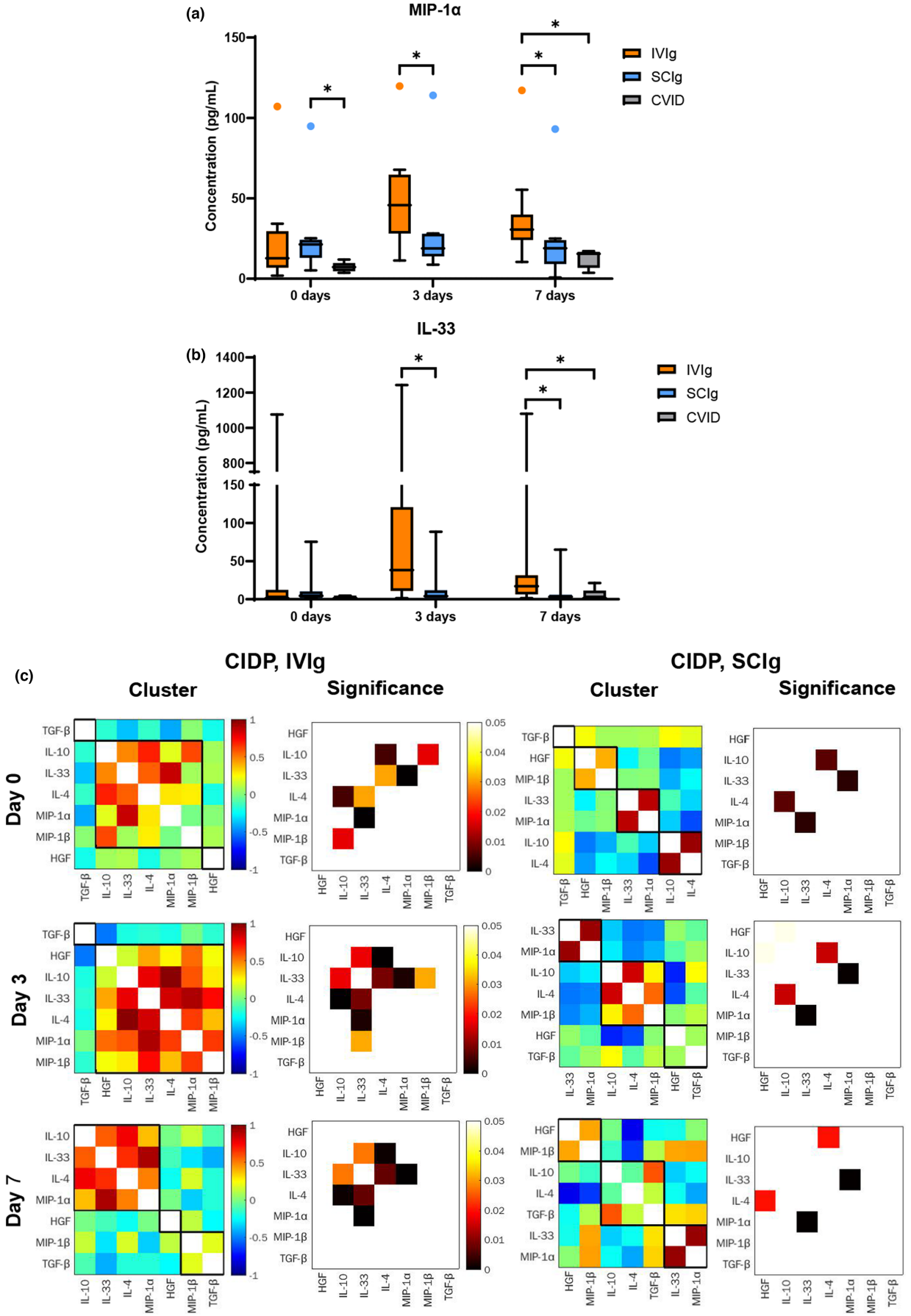
(a)
MIP-1α
Concentration (pg/mL)
150
100
50
0
0 days
3 days
7 days
IVIg
SCIg
CVID
(b)
IL-33
Concentration (pg/mL)
1400
1200
1000
800
150
100
50
0
0 days
3 days
7 days
IVIg
SCIg
CVID
(c)
CIDP, IVIg
CIDP, SCIg
Cluster
Significance
Cluster
Significance
Day 0
Day 3
Day 7
TGF-β
IL-10
IL-33
IL-4
MIP-1α
MIP-1β
HGF
1
0.5
0
-0.5
-1
0.05
0.04
0.03
0.02
0.01
0

FIGURE 3 Cytokine modulation after intravenous immunoglobulin (IVIg) and subcutaneous immunoglobulin (SCIg) infusion in chronic inflammatory demyelinating polyneuropathy (CIDP) patients. CIDP patients showed higher macrophage inflammatory protein (MIP)-1α serum levels than CVID patients, which tended to increase after IVIg infusion and were higher compared to after SCIg infusion, after which MIP-1α serum levels remained stable (a). Interleukin (IL)-33 serum levels were higher after IVIg than after SCIg administration, and compared to CVID patients 7 days after IVIg administration (b). IVIg more broadly modulated cytokine clusters compared to SCIg, most pronounced 3 days post infusion, however, a concordant modulation of IL-33 and MIP-1α was observed in both cohorts (c). $^*p < 0.05$. HGF, hepatocyte growth factor; TGF, transforming growth factor.

the study was conducted in unvaccinated patients during a period of high COVID-19 incidence. However, because a subgroup analysis that excluded patients only providing blood samples at baseline did not relevantly alter our results, and because our results are in concordance with previous studies [17–19, 41], we are confident of their validity.

It should also be noted that immunoglobulin-derived IgG can bind to FcγRs on immune cells and thus interfere with anti-FcγR (CD32a or CD32b/c) flow cytometry antibody binding. Data on this are currently lacking, but all previous flow cytometry-based studies on FcγRs in CIDP were likely to have the same limitation, and since our results align with these studies, we are confident of their validity. Similarly, the fact that activating CD32c can be expressed and is difficult to distinguish from inhibitory $CD32b^+$ on monocytes needs to be considered. However, CD32c is only expressed in 18% of the general population, which makes a significant interference with our results unlikely [25].

Finally, our study did not include therapy-naïve patients, who could exhibit different immune cell profiles after IVIg or SCIg treatment compared to our pre-treated patients. Nevertheless, immune cell patterns in our pre-treated CIDP patients were also concordant with previous studies that included therapy-naïve CIDP patients [17, 18]. Future studies directly comparing immune cells after IVIg and SCIg administration in therapy-naïve and pre-treated CIDP patients are warranted to provide valid data on the influence of recurrent immunoglobulin pre-treatment on immunomarkers of CIDP.

In conclusion, our study indicates that differential pharmacokinetics of IVIg and SCIg result in differential post-infusion cytokine profiles in CIDP patients. There was no evidence for a therapeutically significant differential alteration of immune cells in CIDP.

AUTHOR CONTRIBUTIONS

Martin K. R. Svačina designed and conceptualized the study, collected samples, analyzed and interpreted the data, and drafted and revised the manuscript for intellectual content. Anika Meißner supported study design and conceptualization, collected samples, analyzed and interpreted the data, and drafted and revised the manuscript for intellectual content. Finja Schweitzer and Anne Ladwig supported study design, analyzed and interpreted the data, and revised the manuscript for intellectual content. Kalliopi Pitarokoili and David M. Kofler helped implementing the study, interpreted the data and revised the manuscript for intellectual content. Alina Sprenger-Svačina, Ines Klein, Hauke Wüstenberg, Felix Kohle and Christian Schneider interpreted the data and revised the manuscript for intellectual content. Helmar C. Lehmann designed and conceptualized the study, interpreted the data, and revised the manuscript for intellectual content.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author (Martin K. R. Svačina). The data are not publicly available due to privacy or ethical restrictions.

ORCID

Martin K. R. Svačina https://orcid.org/0000-0001-8166-5132
David M. Kofler https://orcid.org/0000-0001-6164-3980
Alina Sprenger-Svačina https://orcid.org/0000-0002-8883-0492
Felix Kohle https://orcid.org/0000-0002-4429-0367
Helmar C. Lehmann https://orcid.org/0000-0001-6205-2293

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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