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RESEARCH ARTICLE

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Clinical efficacy of *SARS-CoV-2 Omicron*-neutralizing antibodies in immunoglobulin preparations for the treatment of agammaglobulinemia in patients with primary antibody deficiency

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Abstract

Immunocompromised individuals are at significantly elevated risk for severe courses of coronavirus disease 2019 (COVID-19). In addition to vaccination, *severe acute respiratory syndrome coronavirus 2* (*SARS-CoV-2*) neutralizing antibodies (nAbs) have been applied throughout the pandemic, with time of treatment onset and potency against the currently prevailing virus variant identified as relevant factors for medical benefit. Using data from the European Society for Immunodeficiencies (ESID) registry, the present study evaluated COVID-19 cases in three groups of patients with inborn errors of immunity (IEI; 981 agammaglobulinemia patients on immunoglobulin replacement therapy (IGRT); 8960 non-agammaglobulinemia patients on IGRT;

14 428 patients without IGRT), and the neutralizing capacity of 1100 immunoglobulin lots against *SARS-CoV-2* ("Wuhan" and *Omicron* strains), throughout 3 years. From the first (2020/2021) to the second (2021/2022) cold season, i.e., during the virus drift to the more contagious *Omicron* variants, an increase in case numbers was recorded that was comparable (~2- to 3-fold) for all three study groups. During the same period, immunoglobulin lots showed a profound nAb increase against the archetypal *SARS-CoV-2* strain, yet only low levels of *Omicron* nAbs. Notably, shortly before the third (2022/2023) cold season, *Omicron*-neutralizing capacity of released immunoglobulin lots had plateaued at high levels. From the second to the third cold season, COVID-19 cases dropped markedly. While a ~6-fold case reduction was recorded for the groups of non-agammaglobulinemia patients on IGRT and IEI patients not receiving IGRT, the decline was ~30-fold for the group of agammaglobulinemia patients on IGRT. These findings suggest a substantial COVID-19-protective effect of IGRT, at least for distinct groups of antibody-deficient patients.

KEYWORDS

agammaglobulinemia, COVID-19, intravenous immunoglobulin, neutralizing antibodies, primary immunodeficiency, SARS-CoV-2

1 | INTRODUCTION

Neutralizing antibodies (nAbs) are a central component of the immune response against *severe acute respiratory syndrome coronavirus 2* (*SARS-CoV-2*) infection and, therefore, serve as an informative correlate of protection.[1] Conversely, individuals with a reduced or absent antibody response—such as those with agammaglobulinemia—are at significantly higher risk of dying due to coronavirus disease 2019 (COVID-19).[2,3] For this and other conditions belonging to the group of primary or secondary immune disorders (PID, SID), the insufficient levels of circulating functional antibodies can be replenished via treatment with subcutaneous or intravenous immunoglobulins (SCIG, IVIG), highly concentrated immunoglobulin G (IgG) preparations which are produced by plasma fractionation. The antibody spectrum of SCIG and IVIG is a reflection of pathogens and vaccines to which the plasma donor collective had previously been exposed. As thousands of individual donations are pooled to yield a single SCIG or IVIG lot, immunocompromised patients receive a drug that should conceptually protect them against a wide variety of circulating bacterial and viral infections.

This powerful safeguarding approach is, however, challenged when a new pathogen emerges or is subject to mutation. Indeed, it was shown that IVIG preparations released during the first months of the COVID-19 pandemic were lacking any *SARS-CoV-2* neutralization.[4] This was followed by a pronounced potency increase in the second year of the pandemic, first due to the increased fraction of *SARS-CoV-2* convalescent plasma (CP) donors,[5] then additionally because of the broadly rolled out COVID-19 vaccination campaigns,[6] with a delay corresponding to the average time interval of 6 months between plasma donation and release of the corresponding IVIG lot.[5] Yet while *SARS-CoV-2* nAbs in IVIG lots released in the cold season (October to March) of 2021/2022 had already reached substantial levels (i.e., normalized neutralization titers above 1:1000),[7] the question as to which extent protection would be conferred to patients came into focus again due to the emergence of the *Omicron* variant of *SARS-CoV-2*. First detected in November 2021[8] as virus variant most distant (at that time) to the archetypal "Wuhan" strain, several *Omicron* lineages and sublineages have evolved and have dominated infection events since then, owing to their increased contagiousness[9] and high number of accumulated immune escape mutations.[10] The latter fact is also mirrored in the drastically lowered *Omicron*-neutralizing capacity of plasma from *SARS-CoV-2* convalescent individuals, and those twice vaccinated with first-generation COVID-19 vaccines.[11] Correspondingly, a ~20-fold lower potency to neutralize *Omicron* versus the original *SARS-CoV-2* strain was also detected in IVIG lots released in spring 2022.[7]

While high vaccination coverage, adaptation of several vaccines towards *Omicron* and the high degree of *SARS-CoV-2* convalescence have eased everyday life for the general population, the current "post-pandemic" situation is still worrisome for those with immunocompromised medical conditions: with most physical infection prevention measures having been repealed at a global scale, these patients more than ever are in need of effective prophylactic measures. Although the protective level of *Omicron* nAbs is yet to be determined, immunoglobulin replacement therapy (IGRT) could be a vital component of successful prophylaxis for those affected by PID/SID. To shed light on this issue, the present study evaluated a potential negative correlation between COVID-19 incidence decline and neutralizing antibody increase.

2 | MATERIALS AND METHODS

2.1 | IVIG preparations

Analyzed IVIG lots were 10% wt/vol preparations (i.e., 100 mg IgG/mL), either fractionated from plasma collected at Takeda (BioLife) plasma donation centers (source plasma) or obtained from whole-blood donations (recovered plasma). A total of 1001 IVIG lots produced from US plasma donations (Gammagard Liquid; Baxter Healthcare Corp.), and 99 IVIG lots manufactured from plasma of donors residing in central Europe (Austria, Germany, Czech Republic; KIOVIG; Baxter AG), released between March 2020 and February 2023, were tested for *SARS-CoV-2* nAbs. Lots released from January 2022 onwards were additionally tested for nAbs against the *Omicron* variant.

2.2 | Measurement of *SARS-CoV-2 Wuhan* and *Omicron* nAbs

For neutralization assays, wild type (Wuhan) *SARS-CoV-2* strain BavPat1/2020[12] and *Omicron* strain hCoV-19/Netherlands/NH-RIVM-71076/2021 (lineage B.1.1.529; European Virus Archive global [EVAg], REF 014V-04430) were employed. In-house stocks were generated by infection of Vero cells (Cat. No. 84113001, European Collection of Authenticated Cell Cultures, Porton Down, Salisbury, UK) and harvest of the supernatant upon appearance of robust virus-induced cytopathic effects (CPE). In this way, three virus seeds were generated sequentially; seed 3 was used to generate working seeds which were employed for neutralization assays. For neutralization assays, IVIG samples were 2-fold serially diluted in cell culture medium. These dilutions were mixed with an equal volume of virus working seed at $10^{3.0}$ tissue culture infectious doses 50% per milliliter ($TCID_{50}$/mL) and incubated for 150 min at room temperature. Subsequently, the mixtures were added onto Vero cells that had been seeded in 96-well microtiter plates (20 000 cells/well) on the same day. Each sample was analyzed in 10 dilutions with 8 replicate wells per dilution. After incubation for 5–7 days (36°C; humidified atmosphere with 5% CO_2), microscopic readout of CPE was conducted and the neutralization titer (μNT_{50}), i.e., the reciprocal sample dilution resulting in 50% virus neutralization, was determined using the Spearman-Kaerber formula. To enable reliable comparison across distinct assays, normalized neutralization titers (norm. μNT_{50}) were generated via the use of an internal standard (STD; a plasma donation with *SARS-CoV-2* nAbs) that was run in parallel with samples in each assay. Initially, for the STD, a "reference μNT_{50}" was calculated from repeat neutralization assays; to normalize the μNT_{50} of samples from a particular assay, the sample μNT_{50} values were corrected (multiplied) with the ratio of the STD "reference μNT_{50}" and the μNT_{50} of the STD from that assay. Design of the neutralization assays included several validity criteria, i.e., cell viability, confirmatory titration of input virus infectivity, and neutralization testing of an assay control.

2.3 | Retrieval of European Society for Immunodeficiencies (ESID)-registered COVID-19 cases

On November 13th, 2023, the ESID patient registry was queried for COVID-19 cases recorded between January 1st, 2020; and October 23rd, 2023. Retrieved cases were assorted to the following groups: (i) agammaglobulinemia patients on IGRT, (ii) non-agammaglobulinemia patients on IGRT, (iii) patients not receiving IGRT. COVID-19 was ascertained via a positive *SARS-CoV-2* RT-qPCR test for agammaglobulinemia patients or—for the other two groups—via PCR or a serological test. All patients or their legal representatives had given their informed consent (based on IRB approval No. 493/14 of the Ethical Committee Freiburg) to participate in the ESID registry study. Clinical and laboratory data were retrieved from retrospective chart review at the ESID documenting centers and entered online into the registry.[13]

2.4 | Retrieval of COVID-19 cases in general populations

Weekly confirmed COVID-19 cases were exported from the COVID-19 Data Explorer provided on www.ourworldindata.org and summed up for the locations "Europe" and "United States" for the time intervals between October 1st to March 31st, for Fall/Winter seasons of 2021/2022 and 2022/2023, respectively.

2.5 | Data preparation, visualization, and statistical analysis

ESID registry data was extracted and arranged with DbVisualizer Pro (Version 12.0.6). Neutralization assay and ESID registry data were combined using Microsoft Excel (Version 2310); visualization including descriptive statistics was done using GraphPad Prism (Version 8.4.3). Statistical testing was conducted using Minitab.

3 | RESULTS

3.1 | Seasonality of COVID-19 in immunocompromised patient cohorts

A total number of 981 agammaglobulinemia (mostly X-linked agammaglobulinemia) patients receiving IGRT was retrieved from the ESID-registry; the group had a median age of 22 years (range: 0–92 years) and consisted—as expected—mainly of male individuals. The group of non-agammaglobulinemia patients receiving IGRT consisted of 8960 individuals with a median age of 33 years (range: 0–95 years) and a more balanced gender ratio; the most strongly represented disease categories were "Predominantly antibody disorders" (72%) and "Combined immunodeficiencies" (12%). The

group of patients not receiving IGRT consisted of 14 428 individuals with a median age of 20 years (range: 0–93 years), again had a rather balanced gender ratio and a broader dispersion of individuals among disease categories (Table 1). For patients registered within the ESID database, time of COVID-19 infection is documented via the date of the *SARS-CoV-2* RT-qPCR or serological test. Considering the first 2 years of the pandemic, the development of COVID-19 cases per month confirmed the increased disease burden during the colder half of the year, i.e., from October to March (Table 2). For instance, for the patient group without IGRT, 15 COVID-19 cases were recorded in spring and summer of 2020, increasing to 120 cases in the following cold season, dropping again to 37 cases in the subsequent 6 months, and then culminating to 212 cases recorded within October 2021 and March 2022. Similar oscillations were observed for the groups of agammaglobulinemia and non-agammaglobulinemia patients, both under IGRT (Table 2; Figure 1A). Although in the subsequent spring and summer period of 2022, again a drop in cases versus the preceding 6 months occurred, it was less pronounced than before and followed by further decreases up until the end of the period under study.

TABLE 1 Demographic characteristics of patients with primary immune disorders (PID).

Agammaglobulinemia patients on IGRT (AGAMMA + IGRT)	
N (female; male)	981 (65; 916)
median age (range) [year]	22 (0–92)
Non-agammaglobulinemia patients on IGRT (NON-AGAMMA + IGRT)	
N (female; male; unknown)	8960 (4536; 4421; 3)
median age (range) [year]	33 (0–95)
Main disease category	***N* (%)**
Combined immunodeficiencies	1085 (12.1)
Predominantly antibody disorders	6325 (71.6)
Diseases of immune dysregulation	305 (3.4)
Phagocytic disorders	103 (1.2)
Defects in innate immunity	130 (1.5)
Autoinflammatory disorders	50 (0.6)
Complement deficiencies	26 (0.3)
Other well defined PIDs	855 (9.5)
Unclassified Immunodeficiencies	81 (0.9)
Patients without IGRT (NO IGRT)	
N (female; male; unknown)	14 428 (6387; 8040; 1)
median age (range) [year]	20 (0–93)
Main disease category	***N* (%)**
Combined immunodeficiencies	1221 (8.5)
Predominantly antibody disorders	5120 (35.5)
Diseases of immune dysregulation	1308 (9.1)
Phagocytic disorders	1930 (13.4)
Defects in innate immunity	397 (2.8)
Autoinflammatory disorders	855 (5.9)
Complement deficiencies	833 (5.8)
Bone marrow failure	2 (0.0)
Other well defined PIDs	2523 (17.5)
Unclassified Immunodeficiencies	239 (1.7)

Note: Data was retrieved from the ESID registry and assorted to three groups (light blue) based on types of inborn error of immunity and immune replacement therapy (IGRT). Main disease categories were defined based on the International Union of Immunological Societies (IUIS) classification.
Abbreviation: ESID, European Society for Immunodeficiencies.

Over the entire observation time, 513 COVID-19 cases with information on the date of a positive PCR or seroconversion were recorded for patients not receiving IGRT, which accounts for ~4% of the total number of ESID registry entries assorted to that group (14 428; Table 2). This fraction was higher for agammaglobulinemia patients under IGRT (11%; 111 recorded COVID-19 cases, 981 ESID registry entries), with most cases (58, ~50%) recorded during the first *Omicron* season, i.e., at a time where nAb levels were only minor in the general population[11] and in released IVIG lots (Figure 1B). The overall percentage of COVID-19 cases for non-agammaglobulinemia patients under IGRT, for whom IVIG treatment might have more complex effects as antibody deficiencies are less pronounced, was in between the values of the two other studied groups (~9%; 813 recorded COVID-19 cases, 8960 ESID registry entries; Table 2).

3.2 | COVID-19 cases in immunocompromised patients and *SARS-CoV-2 wild type* /*Omicron* nAbs in IVIG

When comparing the first pandemic cold season (October 2020 to March 2021) to the second (October 2021 to March 2022), all three immunocompromised patient cohorts exhibited a rather similar ~2- to 3-fold increase in COVID-19 cases (Table 1). In contrast, from the second to the third cold season (October 2022 to March 2023), a marked reduction in COVID-19 cases occurred, yet to different extent: While a ~6-fold reduction was noted for the group of patients not receiving IGRT (from 212 to 38 cases), the decrease of COVID-19 incidents in the group of agammaglobulinemia patients under IGRT was ~30-fold (from 59 to 2 cases) (Figure 1A and Table 1). The hypothesis of a more prominent reduction in COVID-19 infections in the agammaglobulinemia patients under IGRT group was tested by comparing the annual occurrences against the group of non-IGRT treated patients. The lack of similarity in the ratios of cases was statistically significant (χ^2-test for association; $p = 0.022$; Table 3). For the group of non-agammaglobulinemia patients under IGRT, the decrease was similar to the group of patients without IGRT (~6-fold: from 346 to 58 cases; Table 1). For the groups of patients not receiving IGRT and the group of non-agammaglobulinemia patients under IGRT, the decrease was also quite similar to the drop of

TABLE 2 COVID-19 cases over time in three groups of immunocompromised patients: Agammaglobulinemia with immunoglobulin replacement therapy ("AGAMMA + IGRT"), non-agammaglobulinemia with immunoglobulin replacement therapy ("NON-AGAMMA + IGRT"), no immunoglobulin replacement therapy ("NO IGRT").

YYYY-MM	AGAMMA + IGRT (*N* = 981) COVID-19 incident count (based on positive PCR or serological result)		NON-AGAMMA + IGRT (*N* = 8960)		NO IGRT (*N* = 14 428)		
2020-03	0		3		3		
2020-04	2	***5***	3	***21***	0	***15***	Spring/ summer season 2020
2020-05	0		1		4		
2020-06	2		5		2		
2020-07	0		0		2		
2020-08	1		4		2		
2020-09	0		8		5		
2020-10	4	***22***	25	***166***	9	***120***	Fall/winter season 2020/21
2020-11	4		35		32		
2020-12	5		28		23		
2021-01	3		33		36		
2021-02	1		23		10		
2021-03	5		22		10		
2021-04	0	***3***	22	***37***	12	***37***	Spring/ summer season 2021
2021-05	1		2		10		
2021-06	1		2		7		
2021-07	1		4		1		
2021-08	0		3		2		
2021-09	0		4		5		
2021-10	1	***59***	11	***346***	10	***212***	Fall/winter season 2021/22
2021-11	1		28		12		
2021-12	3		41		22		
2022-01	16		95		60		
2022-02	19		70		58		
2022-03	19		101		50		
2022-04	4	***19***	64	***177***	20	***84***	Spring/ summer season 2022
2022-05	5		26		9		
2022-06	5		26		19		
2022-07	2		31		21		
2022-08	4		15		8		
2022-09	0		15		7		
2022-10	1	***2***	20	***58***	10	***38***	Fall/winter season 2022/23
2022-11	0		9		9		
2022-12	1		10		6		
2023-01	0		5		6		
2023-02	0		5		5		
2023-03	0		9		2		

(Continues)

TABLE 2 (Continued)

YYYY-MM	AGAMMA + IGRT (*N* = 981) COVID-19 incident count (based on positive PCR or serological result)		NON-AGAMMA + IGRT (*N* = 8960)		NO IGRT (*N* = 14 428)		
2023-04	1	***1***	2	***5***	1	***4***	Spring/ summer season 2023
2023-05	0		3		3		
2023-06	0		0		0		
2023-07	0		0		0		
2023-08	0		0		0		
2023-09	0		0		0		
2023-10	0		0		0		
	111		813		513		Total

Note: Data was extracted from the ESID registry and sorted according to date of positive *SARS-CoV-2* test. Sum of cases across six months (either Spring/ summer or Fall/winter season) is highlighted by bold and italic numbers.

Abbreviations: ESID, European Society for Immunodeficiencies; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

infections in the general populations of Europe (~6-fold: from 118 167 912 to 21 001 100 cases) and the United States (~5-fold: from 36 718 131 to 7 914 262 cases). Regarding IVIG lots, while only baseline levels of *SARS-CoV-2* nAbs were present in IVIG released during the first pandemic cold season (October 2020 to March 2021), pronounced anti-*SARS-CoV-2* potency was evident in the second cold season (October 2021 to March 2022), e.g., the mean normalized neutralization titer of all lots released in March 2022 was ~4270 (Figure 1B). This was subject to some further, i.e., approximately 3-fold, increase until the third cold season (e.g., mean normalized neutralization titer of ~12 600 in February 2023). A much more pronounced, ~14-fold increase was, however, evident with respect to *Omicron*-neutralizing capacity, i.e., mean normalized neutralization titers went up from ~270 in March 2022 to ~3870 at the end of the third cold season (February 2023; Figure 1B). In summary, the markedly reduced number of COVID-19 infections amongst immunocompromised patients, particularly those diagnosed with agammaglobulinemia, recorded for the last (third) cold season, coincides with a phase where released IVIG lots present with *SARS-CoV-2* and also *Omicron* nAbs at consistently high levels.

4 | DISCUSSION

From the beginning of the COVID-19 pandemic it has been evident that immunocompromised individuals constitute an especially vulnerable population group, despite the considerable heterogeneity of underlying etiologies. The exceptionally fast development and approval of several COVID-19 vaccines has substantially reduced the global burden of disease, not only in the general population, but also for patients with PID or SID. In this respect, it is important to remember that all of the available COVID-19 vaccines except live vaccines are explicitly recommended for individuals with inborn errors of immunity (IEI).[14] However, longitudinal observations have revealed that, for patients with IEI, there is still a need for additional measures. For instance, a large study on immunocompromised populations versus the general population found that, even though the percentage of immunocompromised individuals vaccinated with ≥3 doses was higher, the rate of severe COVID-19 outcomes was markedly increased, also after adjusting for confounding variables such as age, sex, and the number of non-immunocompromising comorbidities.[15]

Longer and more severe disease courses have also been specifically reported for the subgroup of patients suffering from a primary antibody deficiency (PAD; for review, see Paris[16]). In these subjects, the vaccination-induced antibody response is reduced to variable extent,[17] with *SARS-CoV-2* antibodies, particularly nAbs, being essentially absent for patients suffering from X-linked agammaglobulinemia.[18] A systemic compensation of the missing antibodies is thus indicated especially for this patient subgroup.

During the first 2 years of the pandemic, monoclonal antibodies (mAbs) directed against the *SARS-CoV-2* spike (S) protein were developed and authorized for post-exposure prophylaxis of immunocompromised individuals,[19] as well as treatment.[20] However, the subsequent evolution of the virus, culminating in the global spread of *Omicron*, revealed the fragility of approaches relying on a single or two antigenic determinants, as none of the authorized mAbs was still able to neutralize *Omicron* subvariants that became prevalent in late 2022.[21] Consequentially, all of these mAb preparations are no longer recommended for COVID-19 treatment or prophylaxis.[22]

Even before mAbs were available, COVID-19 patients have been treated with CP, albeit with conflicting results in terms of clinical efficacy. The discrepancies in outcome have meanwhile been linked to the time of treatment onset,[23] and also to the potency level of the administered CP,[24] with early administration of plasma containing high *SARS-CoV-2* nAb levels being most promising. Of note, vaccination induces higher titers than *SARS-CoV-2* infection;[25] thus plasma used for transfusion ideally should be collected from vaccinated, convalescent donors. Given the high levels of both endemic infection and COVID-19 vaccination coverage, the majority

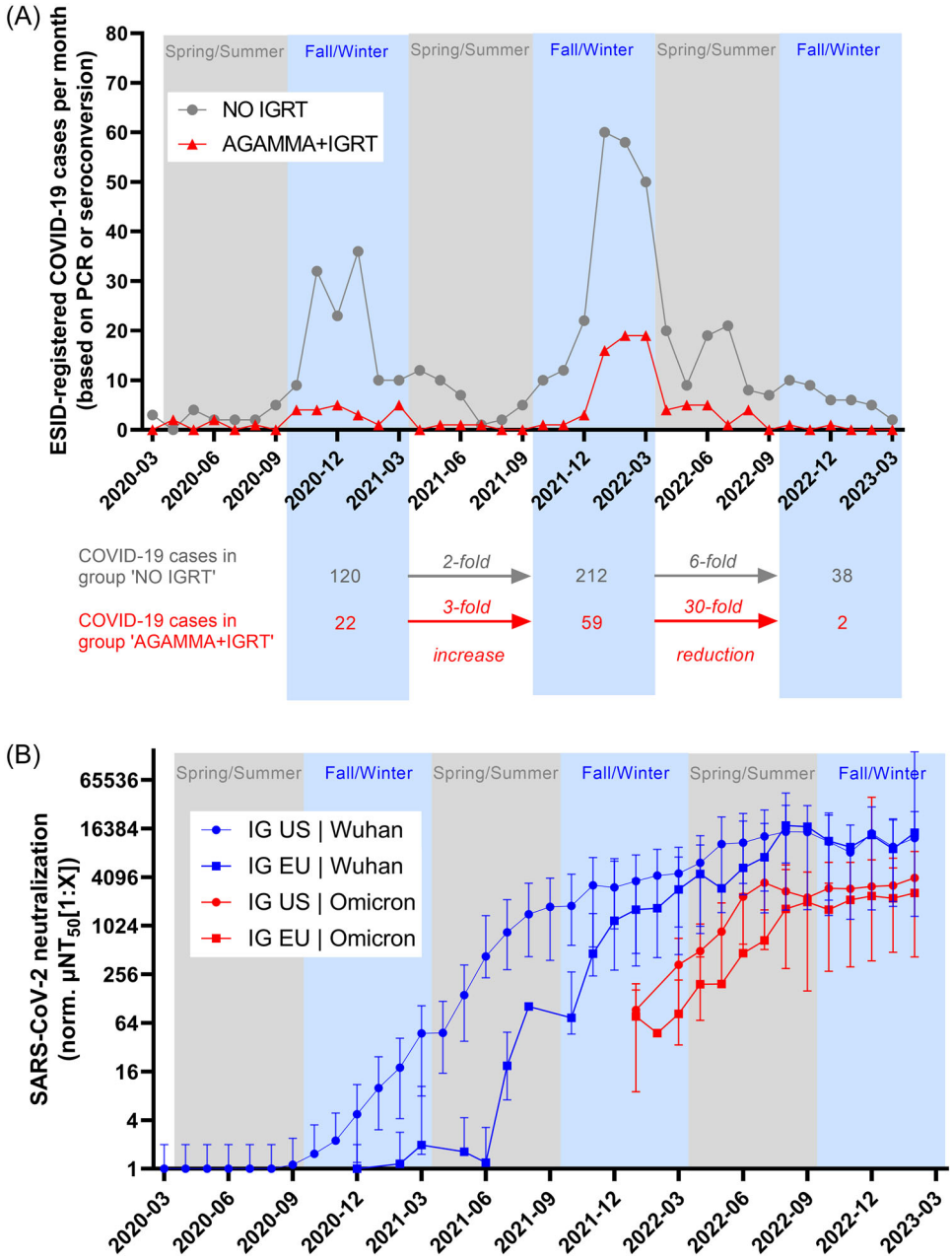

FIGURE 1 Temporal development of COVID-19 cases in subgroups of immunocompromised patients and SARS-CoV-2 neutralizing antibodies. (A) Course of COVID-19 cases among ESID-registered immunocompromised patients over time, shown for agammaglobulinemia subjects on immunoglobulin replacement therapy ("AGAMMA + IGRT"; red triangles) and subjects not receiving Immunoglobulin replacement therapy ("NO IGRT"; gray circles). (B) SARS-CoV-2 neutralizing (blue) and Omicron neutralizing (red) potency of 10% IVIG lots released between March 2020 and February 2023. Subgroups of IVIG manufactured from plasma collected in the US or EU countries are depicted as circles and squares, respectively. Data is shown as geometric means of normalized neutralization titers ±95% confidence interval. COVID-19, coronavirus disease 2019; ESID, European Society for Immunodeficiencies; IGRT, immunoglobulin replacement therapy; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

of individuals donating plasma for fractionation falls into this group. In addition, however, IVIG and SCIG preparations come with a ≥10-fold enriched antibody concentration compared to CP, which—together with their superior safety profile—makes them a preferrable treatment option.

Besides COVID-19 treatment of especially vulnerable groups, the present study argues for a beneficial effect of IGRT in a prophylactic setting for certain groups of patients with IEI, as explained below: One of the main differences between the Fall/Winter seasons 2020/21 and 2021/22 was the shift towards the more contagious *Omicron* variants of *SARS-CoV-2*.[9] Although *SARS-CoV-2* nAbs in IVIG released in the latter period had already reached substantial levels (Figure 1B), these had only limited effect due to the antigenic changes associated with the then-circulating *Omicron*

TABLE 3 Chi-square test for differences in frequency distribution between agammaglobulinemia patients on immunoglobulin replacement therapy (IGRT) and patients not receiving IGRT.

Cold season		Patient group AGAMMA + IGRT	NO IGRT	Total
2020/21	**Count**	**22**	**120**	**142**
	Expected count	*26.02*	*115.98*	
	Contribution to Chi-square	*0.6204*	*0.1392*	
2021/22	**Count**	**59**	**212**	**271**
	Expected count	*49.65*	*221.35*	
	Contribution to Chi-square	*1.7594*	*0.3947*	
2022/23	**Count**	**2**	**38**	**40**
	Expected count	*7.33*	*32.67*	
	Contribution to Chi-square	*3.8747*	*0.8692*	
Total		**83**	**370**	**453**
	Chi-square test	**Chi-square**	**DF**	***p***
	Pearson	**7.658**	**2**	**0.022**

Note: Data was extracted from the ESID registry and assorted to pandemic cold seasons (October to March) of 2020/21, 2021/22, and 2022/23; according to date of positive *SARS-CoV-2* test. Actual case counts and statistical test results are highlighted in bold, while expected counts per subgroup and contribution to Chi-square are shown in italic.

sublineages. Correspondingly, between these two cold seasons, cases recorded in the ESID registry increased similarly, i.e., ~2- to 3-fold, for patients with IEI with and without IGRT (Table 1). In the subsequent Fall/Winter season 2022/23, immune responses to *Omicron* variants had been widely established in the general population, a considerable fraction of which was then also boosted with adapted COVID-19 vaccines. As a consequence, the risk of infection was reduced, which is reflected by the markedly decreased number of ESID-registered COVID-19 cases, when compared to the preceding Fall/Winter season 2021/22, across all of our study groups (Table 1), as well as in the general European and US population. The decrease was approximately 6-fold for the groups of patients with IEI without IGRT and the group of non-agammaglobulinemia patients receiving IGRT, comprising patients who, on average, can be assumed to mount at least a partial antibody response subsequent to infection/vaccination (in contrast to the essentially absent antibody response of patients in the "AGAMMA + IGRT" group). While the ~6-fold decrease of both groups was comparable to the decline in the general population, we recorded a much more pronounced (~30-fold) decline in COVID-19 cases amongst agammaglobulinemia patients with IGRT. The diverging behavior of annual occurrences between the group of AGAMMA + IGRT patients and those not receiving IGRT was significant ($p = 0.022$); and the individual χ^2-contributions indicate that the lower count of infections in the AGAMMA + IGRT group in Fall/Winter 2022/23 is the main driver for the significance (individual χ^2 contribution = 3.9). It is proposed that this discrepancy is at least partly due to IVIG-mediated antibody replenishment in individuals who are largely incapable of mounting an antibody response to pathogens by themselves, as—in contrast to the preceding Fall/Winter season 2021/22—the final cold season examined in our study was the first with a sufficient match between acutely circulating *SARS-CoV-2* variants (i.e., *Omicron*) and the nAb spectrum of IVIG lots released at the same time (Figure 1B).

The fact that only IVIG preparations manufactured by a single company have been analyzed is a limitation of the present work, as the investigated patient groups also received IVIG from other manufacturers. However, in a recent study that evaluated IVIG and SCIG lots from several companies, only minor variation of *SARS-CoV-2* binding antibody levels was shown for different products, while a clear correlation between antibody levels and expiration date (and thus manufacturing date) was found.[26] This is in line with our present and earlier studies[4–7] on *SARS-CoV-2* nAbs. It must further be emphasized that the time between lot release and administration is traditionally short for IVIG, owing to its notoriously insufficient availability, a situation that was even more aggravated during the COVID-19 pandemic.[27] Thus, it can be assumed that IVIG lots with robust *Omicron* nAb levels released during the third pandemic fall/winter season have been administered to patients fast. Since the occurrence of the first *Omicron* variants—such as the B.1.1.529 strain employed in the present study—the virus has seen further development, with BQ.1 and XBB.1.5 variants dominating infections in the third pandemic fall/winter season.[28] However, it has to be noted that the main antigenic changes occurred with the advent of *Omicron*. Further, it is fair to reason that also beyond the end of our study period (February 2023), nAbs against currently circulating *Omicron* sublineages remain high in immunoglobulins, given the recent infections of plasma donors with these "younger" virus types, as well as the rollout of *Omicron*-adapted vaccine variants, both leading to a constant "auto adjustment" of the *SARS-CoV-2* nAb spectrum in IVIG and SCIG.[29]

In addition to the antibody-mediated defense mechanisms against *SARS-CoV-2*, contributions by the cellular adaptive immune system have meanwhile been elucidated. For instance, such T-cell mediated responses were shown to confer cross-variant protection in mice independent of B-cell responses.[30] On the other hand, the importance of antibody-mediated antiviral effects has been demonstrated, e.g., via the high efficacy of treatment of symptomatic infections with S protein-targeting mAbs at a time when the virus had not yet drifted towards *Omicron*.[31] Intuitively, this mechanism is especially important for agammaglobulinemia patients who are not able to mount an own antibody response.

Finally, the retrospective approach of data retrieval from the ESID registry is a limitation of the present endeavor; for instance, a stratification of patients according to number of received COVID-19 vaccinations or treatment with mAbs is not possible as these parameters are not captured within the ESID database. However,

the results presented should be considered to set the base for future prospective investigations, which, for example, could be directed towards pinpointing a protective *Omicron* nAb threshold.

Provided that *Omicron* sublineages will remain dominant, i.e., that the virus is not subject to significant further evolution, the present work supports the notion that IVIG lots released since the end of 2022 are constantly endowed with high neutralizing capacity against circulating *SARS-CoV-2* strains. These levels likely are effective in the prophylactic setting, e.g., when periodically administered as in IEI/PAD, particularly in cases where IVIG and SCIG constitute a treatment well-matched to the pathology, such as for individuals suffering from agammaglobulinemia. Future investigations and maybe clinical trials might further corroborate these findings.

AUTHOR CONTRIBUTIONS

Isabelle Meyts, Mikko R. J. Seppänen, Fabio Candotti, Marta Kamieniak, Thomas R. Kreil, and Markus G. Seidel conceptualized the study. Gerhard Kindle extracted and analyzed data from the ESID registry. Michael Karbiener oversaw laboratory experiments and conducted data analyses. Reinhard Ilk conducted statistical analysis. Michael Karbiener and Thomas R. Kreil drafted the manuscript, with input from Gerhard Kindle, Markus G. Seidel, Isabelle Meyts, Mikko R. J. Seppänen, Reinhard Ilk, Marta Kamieniak, and Fabio Candotti. The ESID-COVID Consortium contributed patient data. All authors approved the final manuscript version for publication.

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CONFLICT OF INTEREST STATEMENT

Michael Karbiener, Reinhard Ilk, and Thomas R. Kreil are employees of Takeda Manufacturing Austria AG, Vienna, Austria, and have Takeda stock interest. Isabelle Meyts has received research funding from CSL Behring (paid to institution) as well as consultancy honorary from Takeda and CSL Behring, paid to Institution. Isabelle Meyts serves on an advisory board for Boehringer-Ingelheim. Marta Kamieniak is an employee of Takeda Development Center Americas, Inc. and a Takeda shareholder. MGS has received research funding from Amgen and Takeda (paid to institution), consultancy honorary from Pharming, Amgen, and Novartis, and a conference travel grant from CSL Behring.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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