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Rising anti-SARS-CoV-2 titer in a human immunoglobulin preparation

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ABSTRACT

Aims: To assess potential changes of pharmacological activities of a novel normal immunoglobulin for intravenous administration from pooled normal plasma (IVIG).

Methods: We assessed the impact of the SARS-CoV-2 pandemic on the level and activity of pathogen-specific antibodies in IVIG batches produced before and during the pandemic. Antibody levels were determined by immunoassays. The functional activity of SARS-CoV-2 antibodies was determined by in vitro neutralization.

Results: In the IVIG, the antibody titer against bacteria, different viruses and a fungus were found to be in a defined range, whereas titers to common pathogens remained consistent over time, the level of antibodies to SARS-CoV-2 have increased within two years after onset of the pandemic to levels comparable to a hyperimmunoglobulin preparation. These antibodies could neutralize SARS-CoV-2 and cross-react with other coronaviruses.

Conclusion: Increasing titers of SARS-CoV-2 antibodies might be beneficial for special vulnerable patient groups.

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INTRODUCTION

Several hundred different, very rare genetic defects can be the cause of primary immunodeficiency, which often are only recognized in adulthood through the occurrence of frequent, particularly severe or even life-threatening infections. Secondary immunodeficiency occurs more frequently and is becoming more common. It can be caused, for example, by specific viruses [human immunodeficiency virus (HIV)] or by certain therapeutic agents, for example, successful immunotherapy, as a complication of the cytotoxic agents used in cancer treatment. On the one hand, immunosuppressants used in transplantation medicine to improve the recipient's tolerance to the transplant. On the other hand, unusual infections occur frequently in all acquired immune deficiency diseases.

For patients with primary immunodeficiency with antibody deficiency, immunoglobulin substitution is the therapeutic standard. In secondary immunodeficiency, prophylactic antimicrobial therapy is usually the first choice. Vaccinations can reduce the risk of infection.

Antibody substitution is mainly considered for those patients in whom infections nevertheless become critically severe or frequent, antibody levels are low (<4 g/L) and there is no adequate vaccine response.

Human immunoglobulin preparations from human plasma are used for substitution therapy. They contain highly purified IgG from plasma coming from healthy donors. Complementary immunological mechanisms contribute to the anti-bacterial [1] and anti-fungal activity of IVIG [2], e.g., through bacterial cell lysis via complement activation, phagocytosis via bacterial opsonization, toxin neutralization, and antibody-dependent cell-mediated cytotoxicity. The antibody specificity and levels in the plasma for fractionation is enriched in the IVIGs. They contain a broad spectrum of antibodies such as virus specific antibodies, e.g., against cytomegalovirus (CMV), varicella-zoster virus (VZV), herpes simplex virus (HSV), hepatitis A virus (HAV), respiratory syncytial viral (RSV), Epstein–Barr virus (EBV), measles, mumps, rubella, parvovirus B19, and polyomavirus BK. The anti-viral effects of IVIG include their activity in preventing cell penetration and activating innate immune system cells and the complement pathways [3].

Intravenous immunoglobulin (IVIG) antigen specificities reflect the antibody diversity in the donor population. For pathogens with a high prevalence in the general population stable antibody titers in IVIGs are observed through natural exposure. In addition, vaccination programs can lead to stable and increased antibody titers in IVIGs, in particular those that are widespread in countries where the most plasma for fractionation is collected. The emergence of SARS-CoV-2 in 2019 and the rapid spread of novel vaccines make it possible to uniquely track the emergence of specific antibodies against a foreign pathogen in the donor population and the IVIGs produced from it.

In this report we characterize virus neutralization and the reactivity of antibodies in Yimmugo (a registered trademark in the European Union and certain other countries, Biotest AG, Dreieich, Germany), a new 10% normal intravenous immunoglobulin G preparation. Specificity against different antigens derived from SARS-CoV-2 as well as related viruses like SARS-CoV, Middle East respiratory syndrome (MERS), and the circulating corona viruses are determined. Since the different strains of SARS-CoV-2 have a high impact on vaccine efficacy the IVIG activity against Spike protein of different variants is analyzed in further detail [4]. The substitution of specific antibodies by IVIG therapy is likely to contribute to the protection of patients with immunodeficiency.

MATERIALS AND METHODS

Human intravenous immunoglobulin preparations

Twenty-three different batches of a new human normal immunoglobulin preparation for intravenous application (IVIG; Yimmugo) produced between 2015 and 2021 were subject of the investigation. A subset of these batches is used for the different analysis methods. The number and production year of used batches is specified in the figure caption. All batches had a protein concentration of 100 g/L with a purity of at least 98% IgG. For the production plasma donations gathered in the EU and the United States were used.

Immunoassays

Binding activities against different pathogens was measured using in-house enzyme-linked immunosorbent assay (ELISA) systems. All ELISA assays were thoroughly tested and suited for the intended purpose. The anti-SARS-CoV-2 titers were determined using an in-house ELISA based on the Spike protein with self-coated plates. All other assays were based on antigen coated 96 well plates (commercially available pre-coated plates as well as self-coated plates) and an anti-human IgG-horseradish peroxidase (HRP) conjugate to detect the bound IVIG product. A specific product standard was used in all assays as reference in order to determine quantitative results.

The ability to opsonize bacterial pathogens (measured for *Escherichia coli*) and reactivity against Rubella antigen were determined using cell based assay with flow cytometry as readout. The assays were developed in-house, thoroughly tested and suited for the intended purpose. A specific product standard was used in all assays as reference in order to determine quantitative results.

The data evaluation used parallel line assay software (PLA 3.0, Stegman systems) resulting in a potency, which was converted to an activity using the predefined standard activity.

Virus neutralization

Virus neutralization against SARS-CoV-2 Wuhan strain was performed by a contract research organization (Texcell, France). The assay was based on cytopathic effect of the virus on mammalian cells. The concentration-dependent ability of IVIG preparations to neutralize the virus and therefore inhibit the cytopathogenic effect (CPE) was compared to an internal standard. This standard was bridged to the SARS-CoV-2 WHO standard and the results were converted to international units (IU/mL).

SARS-CoV-2 variants and other respiratory pathogens

For in-depth analysis of different SARS-CoV-2 variants as well as different respiratory pathogen antigens, the kit systems from mesoscale discovery were used according to the manufacturer's instructions (V-PLEX SARS-CoV-2 Panel 23 Kit, V-PLEX COVID-19 Coronavirus Panel 1 Kit).

RESULTS

Activity against common pathogens

Nineteen different batches of a new IVIG produced between 2015 and 2021 were tested for antibodies against the pathogens with low (hepatitis E virus) to high prevalence. They showed an antibody binding activity against all test antigens. Batch to batch variations were small for common pathogens (Figure 1). Only the anti-hepatitis E activity varies more with up to 14-fold difference.

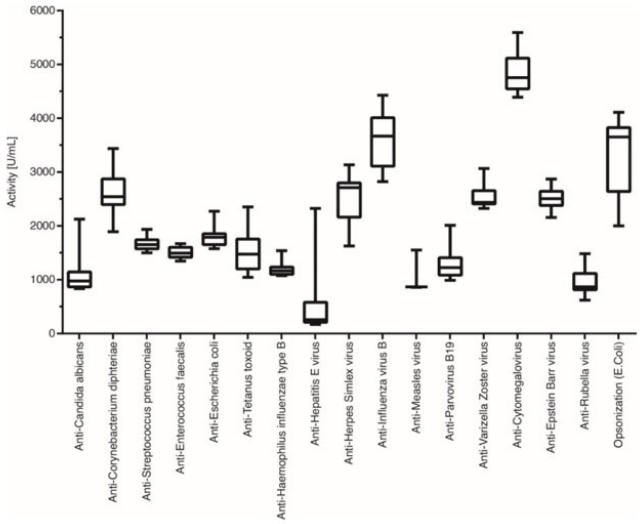

Figure 1: Activities of different IVIG batches against different pathogens. Shown is the IgG activity against the pathogens, listed on the x-axis. Results are shown in arbitrary units. The box plots show the quartiles, minimum and maximum value as well as the median. Dataset from n=19 batches, n=3 batches were produced in 2015, n=7 in 2016, and n=9 in 2021.

In addition to the determination of binding antibodies, in vitro neutralization tests were performed to directly show the ability to block virus attachment, entry and infection as well as to neutralize the toxin. The observed activities were all high enough to provide a protective titer.

Activity against SARS-CoV-2

The SARS-CoV-2 pandemic and the associated global vaccination campaign resulted in the emergence of a new activity in the products. Due to the rise in anti-SARS-CoV-2 antibody activity in the plasma donations, this activity was also reflected in the IVIG batches (Figure 2). Batch 1 was produced in 2017 (pre-pandemic material). All other batches were produced in 2021, while the pre-pandemic material showed no detectable activity, the anti-SARS-CoV-2 activity was constantly rising in 2021. After the impact of the vaccination program in spring 2021 the antibody in the donor population and therefore in the IVIG products were rising with an offset of around six months. This trend was reflected in batches 8–11,

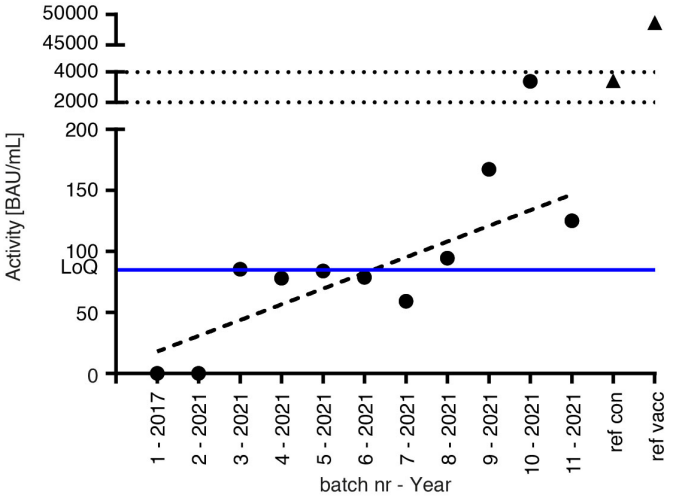

Figure 2: Development of antibody activity against SARS-CoV-2 over time. Dashed line is trendline to show gradual increase, pointed lines are displayed for better visibility and highlight the area where products from convalescent donors are expected, batches 1–7 are below LoQ of the method and therefore extrapolated. Ref con is a reference IgG preparation from convalescent donors (n > 1000 donors); ref vacc is a reference IgG preparation from vaccinated donors (n=2 donors). Batch 1 was produced in 2017 and added as negative control since no anti SARS-CoV-2 activity should be present in this pre-pandemic batch. All other batches were produced in 2021 and are sorted in order of production.

produced in the second half of 2021. Two experimental IVIG preparations were added as a reference. These two preparations produced only from convalescent or vaccinated donor's plasma represent the upper range of the expected activity. It was apparent that vaccinated donors produce around 10 times more antibody activity than convalescent donors, which we could confirm on the single plasma donation level (n=41 vaccinated donors, n=19 convalescent donors, data not shown). The level of the normal IVIG and the hyperimmune preparation from convalescent donors were comparable.

Neutralizing antibodies against SARS-CoV-2

The activity in a cell-based virus neutralization assays with the SARS-CoV-2 Wuhan strain was compared to the binding activity (Table 1). The neutralizing activity was rising with the binding activity. The obtained data also suggest that antibodies from convalescent donors show higher neutralizing activity if correlated to the binding activity, than those from vaccinated donors.

Reactivity against other respiratory pathogens

Although SARS-CoV-2 is a new virus, it belongs to the family of corona viruses and shares some common features with the other family members. Concerning the symptoms of a COVID-19 infection, it resembles those of

Table 1: Anti-SARS-CoV-2 antibody binding activity against S protein in ELISA and neutralizing activity against SARS-CoV-2 (Wuhan strain). Batches are sorted in order of production date.

# - Production year	Binding activity [BAU/mL]	Neutralization [IU/mL]
1 - 2017	0	nd
2 - 2021	0	nd
3 - 2021	86	nd
4 - 2021	78	nd
5 - 2021	84	nd
6 - 2021	79	nd
7 - 2021	59	nd
8 - 2021	95	nd
9 - 2021	168	24
10 - 2021	3378	837
11 - 2021	125	15
Ref convalescent	3419	1645
Ref vaccinated	48745	8740

Abbreviations: BAU: Binding antibody unit; Ref.: reference; nd: not determined.

other respiratory pathogens like influenza virus. To assess cross reactivity the batches were tested against antigens of several respiratory viruses, i.e., different respiratory pathogens as well as the different available SARS-CoV-2 antigens (Figure 3).

Two pre-pandemic batches showed very low signal against all SARS-CoV-2, SARS-CoV, and MERS antigens. This was expected and judged as background signal or natural cross reactivity. Interestingly all batches showed very comparable high-level activity against the circulating corona viruses and influenza. This shows the high prevalence of these viruses in the population as well as the very low cross reactivity between these viruses and the corona viruses causing severe respiratory syndromes (SARS-CoV-2, SARS-CoV, MERS).

Intravenous immunoglobulins from convalescent as well as vaccinated donors showed high reactivity against the spike proteins of Corona viruses causing severe respiratory syndromes. The preparations from vaccinated individuals showed in general a lower reactivity against the SARS-CoV-2 nucleocapsid antigen since the majority of vaccines distributed in the United States and Europe are based on the SARS-CoV-2 spike protein only. Early batches from 2021 showed very low activity against SARS-CoV-2 in the ELISA test, whereas the activity in later batches rose with one batch close to the reference of convalescent donors (Figure 3).

Reactivity against SARS-CoV-2 variants

The SARS-CoV-2 pandemic produces a variety of different virus variants that show different infectivity and a difference in the symptoms and disease outcome. The IVIG batch showed binding activity against all tested variants common in Europe and the United States (Figure 4), whereas the antibodies retained >80% of binding activity against the Delta and Alpha variants, the Omicron variant showed the highest evasion of all variants (20% of the wild type binding activity). A similar prevalence of binding activity could be reproduced with batches of another IVIG product (data not shown).

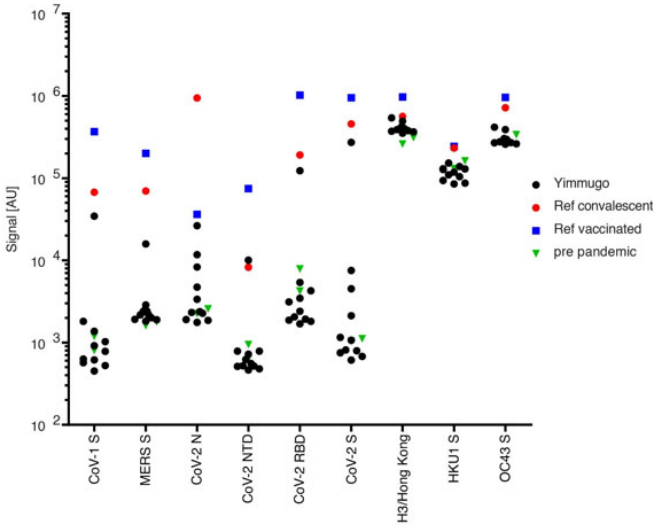

Figure 3: Activity against different antigens of respiratory viruses. Signal of different samples (n=11 batches produced in 2021) against antigens from different Corona viruses and an influenza strain, details are listed in Method section. Antibody preparations solely made from convalescent donors (n > 1000 donors) or vaccinated donors (n=2 donors), respectively as well as two pre-pandemic batches (produced in 2017) are added as reference. CoV = Corona virus; MERS = Middle East respiratory syndrome; S = Spike protein, NTD = N terminal domain (of the Spike protein); RBD = Receptor binding domain (of the Spike protein); H3/Hong Kong = Influenza virus strain; HKU1 = Corona virus strain; OC43 = Corona virus strain.

DISCUSSION

The IVIG production processes including the selection and control of plasma yield batches with a constant biological activity against common pathogens. The observed variabilities are well below the published batch to batch variations for bacterial (up to 11 fold) [5] and viral titers (up to 8 fold) [6]. Larger differences in titers against low-prevalence pathogens, such as hepatitis E virus, are most likely due to heterogeneous seroprevalence depending on the geographical origin of plasma donors [7, 8]. Antibodies against the globally spreading pathogen SARS-CoV-2 appear in the IVIG in this study as well as in other products already after a good year since the start of the pandemic [7]. This matches the simulations based on expected natural infections as well as vaccination programs [9].

It remains to be seen whether high anti-SARS-CoV-2 titers will permanently occur in IVIG products. It could

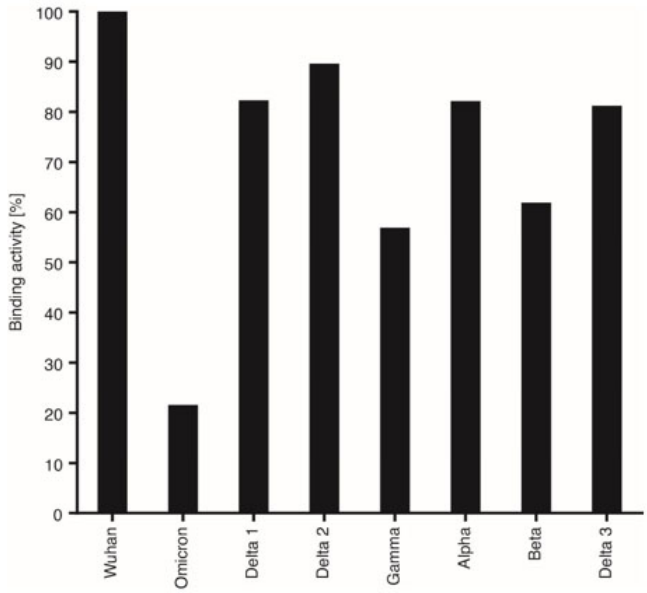

Figure 4: Activity against different SARS-CoV-2 variants. Activity of Wuhan variant is set to 100%, other activities are normalized to this activity. Antigens: Wuhan; Omicron: SARS-CoV-2 Spike (B.1.1.529; BA.1); Delta 1: SARS-CoV-2 Spike (AY.4.2); Delta 2: SARS-CoV-2 Spike (B.1.617.2; AY.4) Alt Seq 2; Gamma: SARS-CoV-2 Spike (P.1); Alpha: SARS-CoV-2 Spike (B.1.1.7); Beta: SARS-CoV-2 Spike (B.1.351); Delta 3: SARS-CoV-2 Spike (B.1.617.2; AY.3; AY.5; AY.6; AY.7; AY.14) Alt Seq 1. The IVIG batch with the highest anti-SARS-CoV-2 Spike activity (10 - 2021) was tested.

also be influenced by vaccination and infection waves. Vaccinated donors have an average 10 times more antibody activity than convalescent donors (own data and [10]). Even a small number of freshly vaccinated donors with high antibody titers could strongly influence the plasma pool level.

Besides the ability to bind virus antigens some reports show the ability of IVIG to neutralize SARS-CoV-2 [11–14] in line with our findings. In accordance with the binding activity, the Omicron variant is reported to be less neutralized by present antibodies [4, 15].

Passive immunization with immunoglobulin preparations is a successful strategy for protecting patients. Transfer of immunoglobulins provides immediate protection against a range of pathogens (for a review see, e.g., [16, 17]). Immunocompromised patients are particularly vulnerable, as they are usually unable to mount a full adaptive immune response and are less likely to benefit from active immunization.

Also for SARS-CoV-2, a direct correlation between binding activity and protection from productive infection by antibodies was reported by Dimeglio [18]. In nursing home residents the neutralizing antibodies reduced mortality and hospitalization [19]. Passive antibody transfer could also be beneficial in primary immunodeficiency, solid organ transplantation or oncohematological patients [20]. As the level of SARS-CoV-2 specific antibodies has only recently increased, this activity should be monitored while evaluating the clinical benefit of such preparations. Clinical data published today with IVIG preparations were likely gathered with product batches manufactured before the observed increase in specific antibodies. The time lag between the first reported cases of infection with a novel virus and the emergence of specific antibodies in IVIG batches is one and a half years, despite the historically uniquely rapid and successful vaccine development. Considering a turnaround time of 6–12 months of the entire production cycle from plasma donation to the final product in patients an important measure for pandemic preparedness may be to establish special donor vaccination and recruitment programs, so that specific antibody preparations can be made available quickly for outbreaks of new viral epidemics.

Our data do not constitute a treatment recommendation. The protective effect of SARS-CoV-2 antibodies may depend on many factors beyond the quantity and quality of pathogen-specific antibodies. Owing to the content of specific IgG antibodies, IVIG may have a benefit, especially if administered after exposure or in the early stages of disease.

The immunomodulatory properties of the antibody molecules may be of greater importance in critically ill patients, as initial clinical data with an IgM-enriched preparation are encouraging [21]. We expect that further clinical trials will provide a better picture of the possibilities of treating COVID-19 with antibodies.

CONCLUSION

Over the course of the coronavirus pandemic, antibody activity against common pathogens remain constant in an IVIG preparation. In contrast, binding activity against SARS-CoV-2 reaches high levels one and a half years after the start of the pandemic and correlates with virus neutralization. All virus variants tested are detected. It has been established for decades that passive transfer of immunoglobulins provides immediate protection against a number of pathogens. Increasing the titer of SARS-CoV-2 antibodies could be beneficial for vulnerable patient populations. Because SARS-CoV-2-specific antibody levels have recently increased, this activity should be monitored when evaluating the clinical benefit of such preparations. While congenital immunodeficiencies are diverse and underdiagnosed, protection of patients by antibody substitution is well established. The number of patients with acquired antibody deficiency, for example as a concomitant of successful drug therapy, is increasing and research into therapy is not keeping pace. Such patients therefore represent a growing and new vulnerable group with high medical need in known and novel infections.

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Authors declare no conflict of interest.

Data Availability
All relevant data are within the paper and its Supporting Information files.

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