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High Viral Specific Antibody Convalescent Plasma Effectively Neutralizes SARS-CoV-2 Variants of Concern

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Abstract:
The ongoing evolution of SARS-CoV-2 variants to omicron severely limits available effective monoclonal antibody therapies. Effective drugs are also supply limited. Covid-19 convalescent plasma (CCP) qualified for high antibody levels effectively reduces immunocompetent outpatient hospitalization. The FDA currently allows outpatient CCP for the immunosuppressed. Viral specific antibody levels in CCP can range ten- to hundred-fold between donors unlike the uniform viral specific monoclonal antibody dosing. Limited data are available on the efficacy of polyclonal CCP to neutralize variants. We examined 108 pre-delta/pre-omicron donor units obtained before March 2021, 20 post-delta COVID-19/post-vaccination units and one pre-delta/pre-omicron hyperimmunglobulin preparation for variant specific virus (vaccine-related isolate (WA-1), delta and omicron) neutralization correlated to Euroimmun S1 IgG antibody levels. We observed a 2- to 4-fold and 20- to 40-fold drop in virus neutralization from SARS-CoV-2 WA-1 to delta or omicron, respectively. CCP antibody levels in the upper 10% of the 108 donations as well as 100% of the post-delta COVID-19/post-vaccination units and the hyperimmunglobulin effectively neutralized all three variants. High-titer CCP neutralizes SARS-CoV-2 variants despite no previous donor exposure to the variants.

Conflict of interest: COI declared - see note

COI notes: TG- paid consultant for Fresenius Kabi; GC and RM are on the Board of Innovative Transfusion Medicine; WB-Board of Blood Centers of America; AC- Scientific Advisory Board of Sabtherapeutics (cow-derived human immunoglobulins COVID-19 treatment and other infectious diseases) and Ortho Diagnostics Speakers Bureau; EB- member of the FDA Blood Products Advisory Committee. All authors report no relevant disclosures.

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Clinical trial registration information (if any):
Convalescent plasma with a high level of virus-specific antibody effectively neutralizes SARS-CoV-2 variants of concern

Short title: Convalescent Plasma Neutralizes Variant SARS-CoV-2

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Abstract

The ongoing evolution of SARS-CoV-2 variants to omicron severely limits available effective monoclonal antibody therapies. Effective drugs are also supply limited. Covid-19 convalescent plasma (CCP) qualified for high antibody levels effectively reduces immunocompetent outpatient hospitalization. The FDA currently allows outpatient CCP for the immunosuppressed. Viral specific antibody levels in CCP can range ten- to hundred-fold between donors unlike the uniform viral specific monoclonal antibody dosing. Limited data are available on the efficacy of polyclonal CCP to neutralize variants. We examined 108 pre-delta/pre-omicron donor units obtained before March 2021, 20 post-delta COVID-19/post-vaccination units and one pre-delta/pre-omicron hyperimmunoglobulin preparation for variant specific virus (vaccine-related isolate (WA-1), delta and omicron) neutralization correlated to Euroimmun S1 IgG antibody levels. We observed a 2- to 4-fold and 20- to 40-fold drop in virus neutralization from SARS-CoV-2 WA-1 to delta or omicron, respectively. CCP antibody levels in the upper 10% of the 108 donations as well as 100% of the post-delta COVID-19/post-vaccination units and the hyperimmunoglobulin effectively neutralized all three variants. High-titer CCP neutralizes SARS-CoV-2 variants despite no previous donor exposure to the variants.
**Key points**

All of the post-delta COVID-19/post vaccination convalescent plasma effectively neutralizes the omicron and delta variants.

High-titer CCP and hyperimmunoglobulin neutralizes SARS-CoV-2 variants despite no previous donor exposure to the variants.
Introduction

Commercial serologic assays predictive of SARS-CoV-2 and variant neutralization are important for effective clinical use of COVID-19 convalescent plasma (CCP), because substantial heterogeneity exists in CCP donor responses with higher antibody levels associated with virus neutralization.\textsuperscript{1-3} The SARS-CoV-2 omicron variant BA.1 rendered many monoclonals ineffective in laboratory virus neutralization tests, necessitating their removal as outpatient monoclonal therapies for acute COVID-19.\textsuperscript{4,5} While Sotrovimab retained activity against omicron BA.1, activity was lost against the BA.1.1 and BA.2 Omicron variants. Tixagevimab/cilgavimab (Evusheld), approved only for post-exposure prophylaxis, was ineffective at neutralizing omicron BA.2 and showed reduced activity towards omicrons BA.1 and BA.1.1.\textsuperscript{6} Bebtelovimab neutralizes omicron BA.1, but will have limited availability.\textsuperscript{7}

A recent large clinical trial over the period from June 2020 to October 2021 demonstrated that early outpatient CCP reduced the risk of hospitalizations by more than half.\textsuperscript{8} Ninety percent of the trial’s 300+ unique CCP donor units were collected prior to January, 2021 representing nonvaccinated pre-alpha/delta/omicron variant plasma. In December 2021, the FDA extended CCP from hospital use to immunosuppressed outpatients, while simultaneously increasing commercial serologic benchmarks by 1.5-fold for CCP qualification.\textsuperscript{9}

Recent omicron variant studies measured virus neutralization without concomitant commercial serologic testing for general antibody levels.\textsuperscript{5} Wang and colleagues measured a 10-fold virus neutralization reduction from SARS-CoV-2 wild type to omicron in 16 individual plasma samples obtained from January to March 2020 in China.\textsuperscript{10} Röllser \textit{et al} examined only 10 CCP units from donors infected with variants and showed a lack of CCP neutralization of
omicron, but substantial neutralization with post COVID-19 post vaccination plasma. These studies have only tested a few samples and do not correlate the results to a commercial assay necessary to qualify therapeutic CCP units. Considering that CCP donors vary significantly in terms of virus neutralization capacity, the use of commercial assays that predict neutralization of SARS-CoV-2 and its variants becomes important to select the optimal therapeutic CCP units.

This study tested a total of 129 samples: 108 CCP donor units, 20 post-delta COVID-19/post-vaccination donor units and one pre-delta/pre-omicron hyperimmunoglobulin preparation for ability to neutralize three SARS-CoV-2 isolates/variants (WA-1, delta, and omicron), correlating results to the Euroimmun spike-S1 antibody plasma level.

Methods

Participants

After the outpatient clinical research trial transfusions from 300+ unique donors were complete, 108 remnant qualified (positive antibody presence after 1:320 dilution using a validated spike protein CLIA ELISA assay) donor plasma units were available for WA-1, delta, and omicron virus neutralizations. 71/108 (66%) pre-delta/pre-omicron units were donated before January, 2021. Approvals were obtained from the Institutional Review Boards at Johns Hopkins University School of Medicine as single IRB for all participating sites and the Department of Defense (DoD) Human Research Protection Office. All participants provided written informed consent. The 20 post-delta COVID-19/post-vaccination (1 J&J- Ad26.COV2.S, 5 Moderna- mRNA-1273 and 14 Pfizer- BNT162b2) plasma aliquots were obtained from Innovative Transfusion Medicine after research informed consent for CCP collection. The collections occurred late August through October 2021 representing delta variant infection. The
viral strain associated to convalescent plasma was associated by timing of donation to existing variants, not sequence confirmed.

The hyperimmunoglobulin sample was prepared from 101 CCP units, collected between June 16, 2020 and January 13, 2021 (representing pre-delta/pre-omicron plasma) from recovered patients by an apheresis plasma collection technique following Mayo Clinic Blood Donor Center’s standard operating procedures. Pooled plasma was loaded on the protein A resin to capture IgG at a neutral pH, washed to remove low affinity proteins and eluted at low pH. Final product was formulated as a 5% protein solution in glycine/acetic acid.

Microneutralization studies

Plasma neutralizing antibodies (nAbs) were determined as described for SARS-CoV-2.\textsuperscript{1,12} WA-1 (SARS-CoV-2/USA-WA1/2020 EPI_ISL_404895) was obtained from BEI Resources while the, delta (hCoV19/USA/MD-HP05660/2021 EPI_ISL_2331507) and omicron (hCoV19/USA/MD-HP20874/2021 EPI_ISL_7160424) variants were isolated from COVID-19 patients at Johns Hopkins Hospital as previously described.\textsuperscript{13} The nAb titer was calculated as the highest serum dilution that eliminated the cytopathic effect in 50% of the wells (NT50) and the area under the curve (AUC) was calculated using Graphpad Prism. The total plasma levels of antibodies against spike region S1 were measured using the ELISA Euroimmun assay as described.\textsuperscript{14}

Results/Discussion

Compared to the WA-1 isolate, we observed a 2- to 4-fold decrease in virus neutralization of delta and 20- to 40-fold neutralization decrease of omicron in all plasma samples (108 pre-delta/pre-omicron CCP units, the 20 post-delta COVID-19, post vaccination units and pre-delta/pre-omicron hyperimmunoglobulin) (Fig. 1). The 108 research trial remnant
units with Euroimmun AU over 3.5 have an 85% rate of positive virus neutralization for WA-1 and delta. However, Euroimmun over 10 AU was necessary to retain similar neutralization for omicron (Fig.1). All of the post-delta COVID-19/post-vaccination donor plasma as well as the hyperimmunoglobulin, with Euroimmun AU over 10 effectively neutralized the WA-1 isolate, delta and omicron variants. As a benchmark for clinical effectiveness, the early treatment CCP trial, successful at preventing hospitalizations principally with unvaccinated ancestral virus, had more than 10% of pre-delta/pre-omicron 2020 prevaccination donor units or 2021 donor units with Euroimmun AU over 10 (Fig 1). For all these clinical trial transfused units, the WA-1 neutralizing antibody geomean was 26 IU/mL, while remnant 108 CCP plasma units had a geomean of 28 IU/mL. However, sorting to increasing Euroimmun AUs from greater than 3.5, to 7 and to 10 AUs, increased two-fold and ten-fold respectively WA-1, delta and omicron neutralization (Fig 2). All of the post-delta COVID-19/post vaccination samples measured Euroimmun AU over 10, with WA-1 neutralization at geomean 1598 with comparable reduction in delta activity of two-fold and 20-fold with omicron (Fig. 2). The pre-delta/pre-omicron hyperimmune globulin IgG showed a similar fold decrease in neutralization across the three isolates (Fig. 2). The wider span of both high and low levels of neutralization antibodies in CCP may account for the larger decrease in delta activity compared to the narrower high range of virus neutralizations with the post-delta COVID-19/post-vaccination units. This data suggests that Euroimmun AU over 5 (~1.5X3.5) would be effective for delta and over 10 (~3X3.5) for omicron CCP therapy.

Commercial serologic assays were adjusted approximately 1.5-fold by the FDA to be in the effective range for omicron. The Euroimmun assay is one of many that can be utilized for
donor plasma qualification. Many published studies on variant virus neutralization by CCP characterize 10 to 30 individual donors deeming them inactive against variants with small sample sizes. In contrast, here we compared over 100 CCP donor units to show that high viral specific antibodies defined by commercial serologic tests indicates omicron neutralization. The post-delta COVID-19/post-vaccination donor units and hyperimmune globulin retain broad activity against variants through omicron indicating the improved potential efficacy of a polyclonal antibody treatment compared to monoclonal antibody treatments as a way to keep up as a therapeutic tool against the evolving virus. This study did not characterize omicron convalescent plasma neutralization of older variants. Another limitation is use of only in-vitro data for which the true relevance to clinical use is not known. We posit that high titer polyclonal CCP donors characterized with commercial serologic assays with a mismatch to existing variants still neutralizes SARS-CoV-2 variants as well as lower titer donor plasma units with a direct match of plasma to virus variants. These polyclonal high titer units and hyperimmune globulin retain efficacy as antibody therapy in the face of variants.

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Authorship

Contribution: DS, AC, AP, TG & AT designed experiments; ML, CW, CB, AP, EB, YE performed experiments; MJ, TW and AD purified the hyperimmunoglobulin; GC, WB and RM provided post-delta COVID-19, post-vaccination plasma; AY, KL managed trial research blood bank; AS, EB, TG were contributing blood bankers; EC, BM, MH, YF, BP, SH, AL, JP, SA, JG contributed to the conduct of the related clinical trial, DS, KG, DH, EB, AT and SS organized clinical trial studies as source of CCP; DS, ML, AP analyzed data and wrote the manuscript with input from all authors and all authors approved the final version of the manuscript. The full COVID-19 Serologic Studies Consortium (CSSC) authors are listed in the appendix.

Conflict-of-interest disclosure: TG- paid consultant for Fresenius Kabi; GC and RM are on the Board of Innovative Transfusion Medicine; WB-Board of Blood Centers of America; AC- Scientific Advisory Board of Sabtherapeutics (cow-derived human immunoglobulins COVID-19
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Figure Legends

**Figure 1 Reduction in virus neutralization sorted by plasma type as well as an increase by Euroimmun antibody levels.** A) WA-1, delta and omicron virus microneutralization sorted by the 108 CCP units, post-delta COVID-19, post vaccination and hyperimmunoglobulin. IU/mL geometric means are shown above x-axis. B) Antibody levels over 3.5 Euroimmun AU show 85% microneutralization with WA-1 and delta while omicron neutralization requires Euroimmun AU over 10 for 85% of the 108 CCP donors. Post-delta COVID-19/post vaccination retains 100% virus neutralization for the three variants. Virus neutralization is any positive IU/mL over 1. C) Range of Euroimmun antibody levels sorted by prevaccination 2020 donor collections and early January to March 2021 for the large number of clinical trial donors and the 108 remnant donors. Means near x-axis and number above 10 AU in red above values. More than 10% of units have Euroimmun AU over 10 except for the 2020 remnant units. Three of the 12 2021 108 donors were vaccinated along with documented COVID-19. The vaccine status of the other 9 was not recorded at time of donation. The p values were Tukey’s multiple comparisons of one way ANOVA-****p<0.0001;***p<0.001; **p<0.01.

**Figure 2 Sorting higher Euroimmun categories indicates virus neutralization to WA-1, delta and omicron.** WA-1 (A), delta (B) and omicron (C) virus microneutralization measured in CCP, post-delta COVID-19/post-vaccination and hyperimmune globulin (HIG) sorted for viral-specific antibody levels by Euroimmun arbitrary units (AU) at 1:101 dilution. IU/mL geometric means are shown above x-axis. The p values were Tukey’s multiple comparisons of one way ANOVA-****p<0.0001;***p<0.001; **p<0.01; *p<0.05.
