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Case Report

Pharmacokinetics of convalescent plasma therapy in a COVID-19 patient with X-linked Agammaglobulinemia[☆]

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A B S T R A C T

Convalescent plasma (CP) has been the first line of defense against numerous infectious diseases throughout history. The COVID-19 pandemic created a need for a quick, easily accessible, and effective treatment for severe disease and CP was able to meet that immediate need. The utility of CP warrants a better understanding of the pharmacokinetics of CP treatment. Here we present the case of a COVID-19 patient with a genetic deficiency in antibody production who received CP as a part of the treatment regimen. In depth serological analysis revealed a surprising lack of SARS-CoV-2 specific antibodies and reduced serum IgG following CP infusion. Our study highlights plasma dilution and accelerated antibody clearance as potential mechanisms for the variable efficacy of CP therapy.

Introduction

Historically, convalescent plasma (CP) has been used to treat the effects of numerous infectious diseases including those caused by *Clostridium tetani*, *Corynebacterium diphtheriae*, influenza, respiratory syncytial virus, SARS-CoV, and Ebola virus [1,2]. Modern invention of antimicrobials, vaccines, and monoclonal antibody therapy has largely replaced the need for CP. However, the speed at which the COVID-19 pandemic progressed created an immediate need for specific and effective therapies to treat severe cases of COVID-19, and CP was able to fill that void [1]. The recent advent and distribution of highly effective SARS-CoV-2-specific monoclonal therapies and vaccines have begun to replace the need for convalescent plasma therapy in the developed world [3–6]. However, the emergence and dominance of the highly mutated SARS-CoV-2 variant B.1.1.529 has the potential to significantly lessen the efficacy of the current COVID-19 vaccines and monoclonal antibody therapies [7]. In addition, CP also remains a viable treatment in resource poor settings where sourcing effective, yet inexpensive and convenient treatments is of paramount importance [8]. Therefore, understanding the contribution of CP therapy to the overall SARS-CoV-2 antibody pool is valuable for understanding the treatment of pa-

tients with COVID-19, as well as other disorders for which CP may be indicated.

X-linked agammaglobulinemia (XLA) is an inborn error of immunity in which a genetic defect in B cell development results in the lack of peripheral B cells and antibody production. These patients are particularly susceptible to extracellular bacterial and enveloped viral RNA infections thus requiring regular supplementation of passive immunotherapy in the form of intravenous immunoglobulin (IVIG) to remain healthy [9]. In the context of the recent COVID-19 pandemic, IVIG pools are unlikely to provide specific immunity to SARS-CoV-2 making convalescent plasma an important treatment for such patients [10]. Due to the lack of endogenous antibody production in XLA patients, the impact of COVID-19 CP can be measured directly. In contrast, the impact of CP to the overall antibody pool is difficult to determine in immunocompetent COVID-19 patients, as antibodies derived from CP cannot be distinguished from the patient's own antibody response. Here, we present a case of COVID-19 from March 2020 in a 39-year old male with XLA that was treated with 2 doses of convalescent plasma. In-depth serological testing of the XLA recipient serum revealed a marked global deficiency in SARS-CoV-2 specific antibody a mere week following CP infusion.

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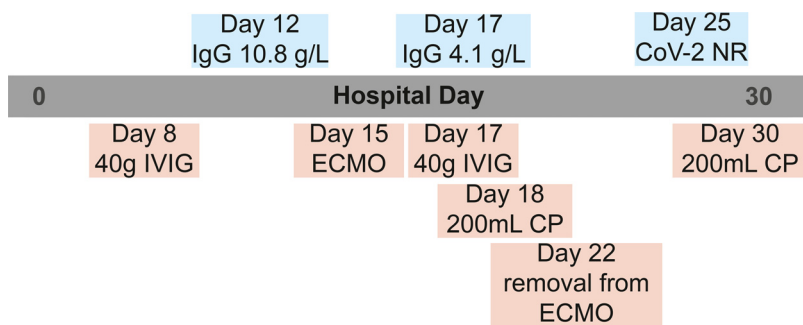


Fig. 1. Timeline of Treatments and Laboratory Results: Laboratory results (blue) and clinical treatments (red) from hospital days 0 through 30. Convalescent plasma (CP), Intravenous Immunoglobulin (IVIG), Non-reactive (NR), Extracorporeal Membrane Oxygenation (ECMO).

Materials and methods

Expression and purification of SARS-CoV-2 RBD

The amino-acid sequence of the SARS-CoV-2 Spike glycoprotein sequence (GenBank: MN908947) was used to design a codon-optimized version for mammalian cell expression. The synthetic gene encoding the receptor binding domain (RBD) a.a.319–541) was cloned into pcDNA 3.1 Myc/His in-frame with c-Myc and 6-histidine epitope tags that enabled detection and purification. The cloned genes were sequenced to confirm that no errors had accumulated during the cloning process. The construct was transfected into Expi293 cells using ExpiFectamine 293 Transfection Kit (Thermo Fisher). Recombinant proteins were purified by immobilized metal chelate affinity chromatography using nickel-nitrilotriacetic acid (Ni-NTA) agarose beads, eluted from the columns using 250 mmol/L imidazole, and then dialyzed into phosphate-buffered saline (PBS), pH 7.2. Proteins were checked for size and purity by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE).

SARS-CoV-2 specific microsphere immunoassay (MIA)

Specimens were assessed for the presence of antibodies reactive with SARS-CoV-2 using an MIA [11]. Recombinant SARS-CoV-2 nucleocapsid, and RBD were covalently linked to the surface of fluorescent microspheres (Luminex Corporation). Serum samples (25 μ L at 1:100 dilution) and antigen-conjugated microspheres (25 μ L at 5×10^4 microspheres/mL) were mixed and incubated 30 min at 37 $^{\circ}$ C. Serum-bound microspheres were washed and incubated with phycoerythrin (PE)-conjugated secondary antibody. The PE-conjugated antibody was chosen to specifically recognize total Ig (Pan-Ig; Southern Biotech # 2010-09; IgM #2020-09; IgA #2050-09; IgG1 #9054-09; IgG3 #9210-09). After washing and final resuspension in buffer, the samples were analyzed on a FlexMap 3D analyzer using xPONENT software, version 4.3 (Luminex Corporation).

Plaque reduction neutralization assay (PRNT)

For the detection of SARS-CoV-2 neutralizing antibodies, 2-fold serially diluted test serum (100 μ L) was mixed with 100 μ L of 150–200 plaque forming units (PFUs) of SARS-CoV-2 (isolate USA-WA1/2020, BEI Resources, NR-52281) and incubated for 1 h at 37 $^{\circ}$ C, 5% CO₂. The virus:serum mixture (100 μ L) was applied to VeroE6 cells grown to 95–100% confluency in 6 well plates. Adsorption of the virus:serum mixture was allowed to proceed for 1 hour at 37 $^{\circ}$ C, 5% CO₂. Following the adsorption period, a 0.6% agar overlay prepared in cell culture medium (Eagle's Minimal Essential Medium, 2% heat inactivated FBS, 100 μ g/ml Penicillin G, 100 U/ml Streptomycin) was applied. Two days post-infection, a second agar overlay containing 0.2% neutral red prepared in cell culture medium was applied, and the number of plaques in each sample well were recorded after an additional 1–2 days incubation. Neutralizing titers were defined as the inverse of the highest dilution of

serum providing 50% (PRNT50) or 90% (PRNT90) viral plaque reduction relative to a virus only control. This assay has been described and is considered the standard for the determination of neutralizing virus-specific titers [12–14].

Results

Case presentation and clinical course

The patient is a 39-year old man with a history of X-linked agammaglobulinemia (XLA) who presented with acute onset of fever, dyspnea, and hypoxia. A nasopharyngeal swab was positive for the presence of SARS-CoV-2 by Abbott real-time SARS-CoV-2 PCR, confirming a diagnosis of acute COVID-19. Upon hospital admission, the patient was treated with supplemental oxygen, hydroxychloroquine, azithromycin, dexamethazone, tocilizumab, and therapeutic anti-coagulation. On hospital day 8, the patient received 40g intravenous immunoglobulin (IVIG) according to his normal schedule (Fig. 1). Despite multiple treatments and supportive therapies, the patient continued to deteriorate, suffering from progressive severe hypoxemic respiratory failure that required mechanical ventilation, and ultimately venovenous extracorporeal membrane oxygenation (ECMO). Laboratory testing at hospital day 12 revealed a total serum IgG concentration of 1079 mg/dL that fell to a remarkably low level of 406 mg/dL (< 1000 mg/dL [15]) 5 days later. Due to low serum IgG, the patient received an additional 40g of IVIG on hospital day 17. On hospital day 18, the patient was able to receive 1 unit (211 mL) of CP as part of the Mayo Clinic Expanded Access Protocol. The patient experienced a transient improvement of respiratory mechanics, which allowed for ECMO decannulation on hospital day 22 while still requiring ventilator support. However, one week following CP therapy (day 25), SARS-CoV-2 specific antibodies were undetectable. Therefore, the patient received an additional unit (200 mL) of CP on hospital day 30 through FDA authorization of single patient investigational new drug. Unfortunately, the patient had further respiratory deterioration and eventually succumbed to his disease.

In-depth serological analysis of convalescent plasma donor/recipient pair

Specimens from the plasma donor (time of donation) and the XLA recipient (1-week post-infusion) were tested for total Ig antibody reactivity to SARS-CoV-2 antigens. Testing by a clinical microsphere immunoassay (MIA) (Emergency Use Authorization: <https://www.fda.gov/media/137541/download>) resulted in a robust signal for SARS-CoV-2 specific antibodies (N MFI = 34410 and RBD = 25899) and virus neutralizing titers (PRNT50 \geq 640; PRNT90 = 80 for the donor plasma (Table. I). In contrast, SARS-CoV-2 reactive antibodies were not detected in the recipient serum using the same assay. The surprising lack of SARS-CoV-2 specific antibodies in the recipient prompted further in-depth testing of both the donor plasma and the recipient serum. Rather than performing the MIA at the standard specimen dilution of 1:100, a dilution series

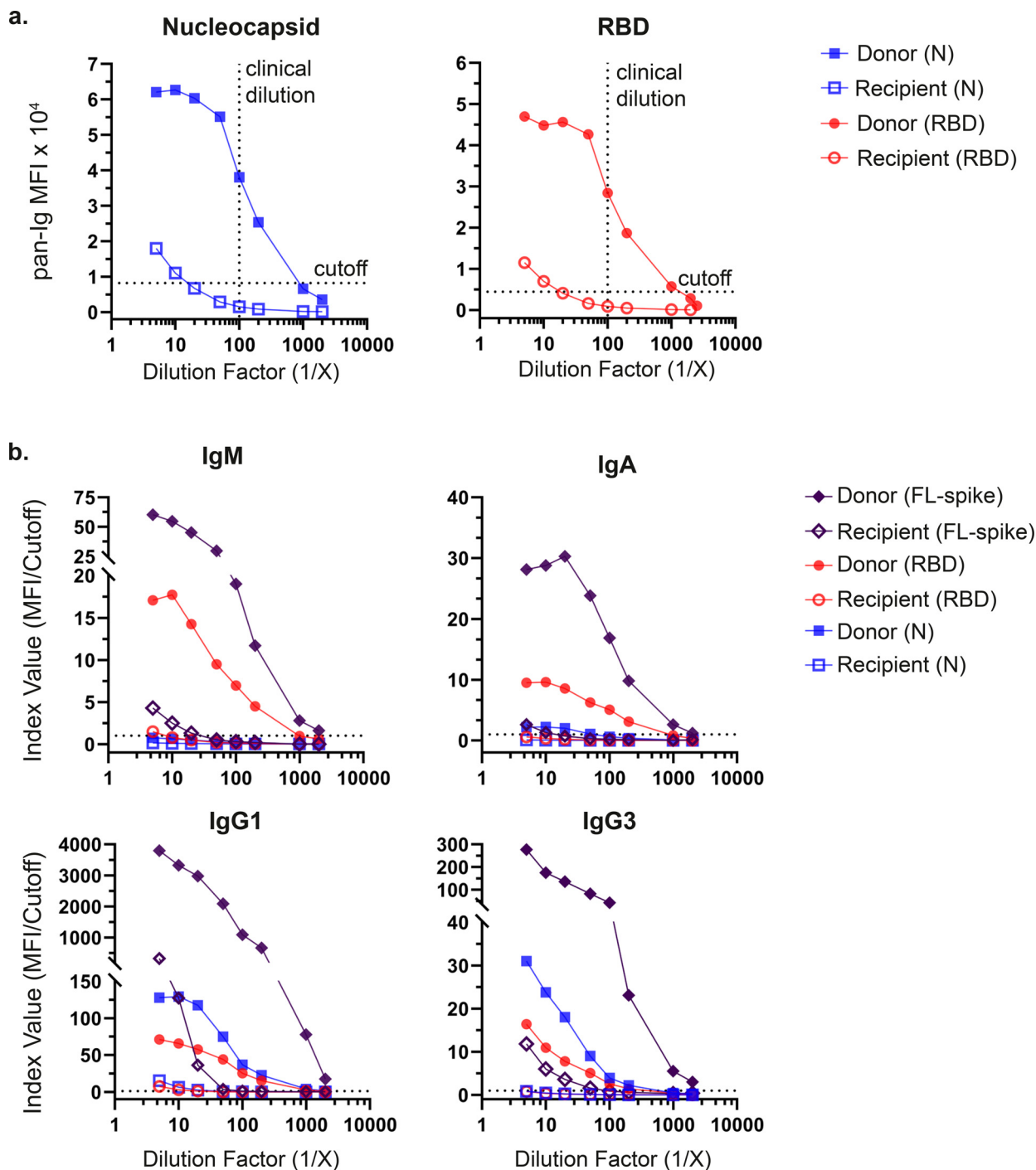


Fig. 2. Dilution Curves of Donor Plasma and Recipient Serum: Donor plasma (closed symbols) and recipient serum (open symbols) specimens were analyzed for (a) total Ig or (b) IgM, IgA, IgG1, IgG3 reactivity to SARS-CoV-2 nucleocapsid and RBD by a microsphere immunoassay. Antigen-specific reactivity was tested for each specimen diluted from 1:5 through 1:2000 and reported as median fluorescence intensity (MFI) $\times 10^4$. Dashed lines indicate the clinical reactivity cutoff, and the clinical assay dilution, respectively.

Table 1
SARS-CoV-2 reactivity and neutralizing ability in the donor/recipient pair.

	N (MFI)	RBD (MFI)	Clinical Result	PRNT50	PRNT90
Donor	34410.0	25899.0	Reactive	≥ 640	80
XLA Recipient	682.0	451.5	Non-Reactive	n/a	n/a

was performed on the specimens starting at a 1:5 dilution with serial dilutions through 1:2000 (Fig. 2a). Interestingly, low-level SARS-

CoV-2 specific Ig reactivity was detected in the recipient serum at both the 1:5 and 1:10 dilutions (N MFI = 17957, 11050; and RBD MFI = 11512, 6930), but not at the standard clinical assay dilution of 1:100. In contrast, the donor plasma contained high-level SARS-CoV-2 specific Ig reactivity seen at the same dilutions of the recipient serum (N MFI = 62083, 62675; and RBD MFI = 46980, 44822). Area under the curve (AUC) analysis was performed to directly compare the SARS-CoV-2 antigen reactivity of the donor plasma (N = 2599.0; RBD = 2112.0) and XLA recipient serum (N = 108.0; RBD = 60.2) over the entire dilution curve, revealing a 24- and 35-fold reduction in

Table 2
In-depth serological analysis of SARS-CoV-2 specific antibodies in the donor/recipient pair.

Antigen	Antibody	Donor (AUC)	Recipient (AUC)	Fold Reduction
Nucleocapsid	IgM	145.1	52.9	2.7
	IgA	419.2	21.3	19.7
	IgG1	23,687.0	163.3	145.1
	IgG3	2,780.0	40.9	68.0
RBD	IgM	4,567.0	90.9	50.2
	IgA	3,180.0	37.0	85.9
	IgG1	14,930.0	68.8	217.0
	IgG3	1,763.0	44.9	39.9
Full-Length	IgM	12,668.0	188.0	67.4
	IgA	10,462.0	152.3	68.7
Spike	IgG1	635,525.0	3,336.0	190.5
	IgG3	27,953.0	1,108.0	25.2

N- and RBD-specific antibody levels between the donor and recipient, respectively.

To better characterize the SARS-CoV-2 specific antibody profile in both the donor and XLA recipient, we performed serial dilution assay to detect IgM, IgA, IgG1 and IgG3 reactivity to the N protein, RBD, and full-length (FL) spike protein. The highest signals for antibody reactivity in the recipient plasma were seen for the FL-Spike antigen in all isotypes/subclasses, followed by RBD for IgM and IgA, then nucleocapsid for IgG1 and IgG3 (Fig. 2b). Overall, the donor antibody pool was dominated by IgG, with IgG1 being more prominent than IgG3. This pattern of antibody reactivity was largely mirrored in the XLA recipient, albeit at markedly reduced levels. As seen with total Ig, there was considerably less reactivity to SARS-CoV-2 seen in the recipient serum than the donor plasma for all isotypes, IgG subclasses, and antigens tested. The largest decreases in SARS-CoV-2-specific antibody in the XLA recipient was seen for the most dominant subclass – IgG1, with an approximately 200-fold reduction in AUC measurements for all antigens within 1 week of infusion (Table 2). The next largest decrease measured was an approximately 70-fold reduction in SARS-CoV-2 specific IgA, followed by IgM and IgG3. Together, our results show markedly low levels of SARS-CoV-2-specific antibody in an XLA recipient patient one week following CP infusion.

Discussion

The goal of this study was to gain insight into the contribution of CP to the recipient antibody pool and potential efficacy of the treatment. We present a rare case of an individual with XLA who received CP as part of his treatment regimen for severe COVID-19. One week following CP infusion SARS-CoV-2 specific serum antibodies were undetectable using our standard clinical SARS-CoV-2 MIA. The lack of SARS-CoV-2 reactivity in the XLA recipient is curious and likely due to multiple factors.

First, we consider the simple principle of a dilution effect. Assuming a typical adult has a blood volume of ~5 liters, then 1 unit of plasma (200 mL) would be equal to a 25-fold dilution of the donor plasma in the context of the recipient blood volume. When the AUC measurements from our semi-quantitative clinical SARS-CoV-2 MIA are compared, we do in fact measure a 24- to 35-fold reduction in Ig reactivity to N and RBD, respectively. However, this does not account for the >200-fold reduction seen in IgG1 reactivity to SARS-CoV-2 antigens 7 days following CP infusion. In fact, several COVID-19 positive XLA patients that received CP did have detectable SARS-CoV-2 virus neutralization and antibody reactivity following infusion [16,17]. Therefore, plasma dilution alone is unlikely to account for the dramatic decrease in SARS-CoV-2 reactivity in our XLA recipient patient.

Next, we consider accelerated clearance of antibody as the potential cause of lower-than-expected SARS-CoV-2 reactivity. It is well known that convalescent plasma containing higher pathogen-specific titers are

correlated with better outcomes following CP therapy. However, the pharmacokinetics of passively administered immunoglobulins are variable and highly dependent on isotype/subclass interactions with Fc receptors, glycosylation status, and antigen load [1,18,19]. The lack of SARS-CoV-2 reactivity in the XLA patient 5 days following CP infusion may suggest quick consumption SARS-CoV-2 specific antibodies. We speculate that a high SARS-CoV-2 antigen load present during acute, severe disease could consume the specific antibody through immune complex formation and subsequent clearance [20,21]. In addition, the XLA recipient also experienced faster than expected clearance of IVIG-derived IgG with a 2.7-fold decrease in total IgG within 5 days, rather than the typical IgG serum half-life of approximately 21-days [19]. A similar phenomenon of accelerated IgG clearance was seen by Milošević and colleagues who reported a case of COVID-19-positive XLA patient who required multiple doses of both IVIG and convalescent plasma due to continuously low levels of IgG and the absence of SARS-CoV-2 reactivity upon laboratory testing [22].

Despite significant medical intervention, the XLA patient in this study eventually succumbed to severe complications from COVID-19. Other XLA patients have survived COVID-19, both with and without convalescent plasma therapy [10,16,17,23–27]. Despite our laboratory analysis, we are unlikely to determine a precise cause of the poor COVID-19 disease trajectory in our case. However, this unique case of COVID-19 in an XLA patient has revealed the potential for accelerated clearance of total and virus-specific IgG that would otherwise be masked by antibody production in immunocompetent patients. Therefore, we conclude that accelerated IgG clearance and antibody dilution should be considered when evaluating the efficacy of CPT in immunocompromised patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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