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Polyclonal immunoglobulins for COVID-19 pre-exposure prophylaxis in immunocompromised patients

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ABSTRACT

Immunocompromised patients remain at high risk of COVID-19 morbidity and mortality. After recent Omicron sublineages gained full resistance to Evusheld™, they are left without effective pre-exposure prophylaxis. We review here arguments to support the growing role of regular immunoglobulin (IG) infusions at protecting against COVID-19. Since there is evidence for neutralizing antibody titers approaching the ones seen in hyperimmune sera, and since some categories of patients at risk for COVID-19 progression are already under pre-exposure prophylaxis with IG, this cost-effective strategy should be urgently investigated in randomized clinical trials. Surveys of anti-Spike antibody levels in current plasma donations are urgent to forecast the potency of future IG batches.

Immunocompromised (IC) patients represent a cohort at increased risk for a severe disease course after opportunistic infections, and which often does not mount a protective immune response after specific vaccinations. In addition, they often have comorbidities contraindicating long-term usage of small molecule antivirals, making them eligible to passive immunotherapies only.

For such reason many severe IC patients are regularly administered polyclonal standard immunoglobulins (IG) as pre-exposure prophylaxis (PreEP), either intravenously (IVIG) or subcutaneously (SCIG): in fact, regular plasma donors are mostly immunocompetent subjects who have been either vaccinated against or are convalescent from common infectious diseases, and as such retain high-titres of neutralizing antibodies (nAb) against many different pathogens.

SARS-CoV-2 also represents a life-threatening infection for IC patients [1], but, being a recent virus with poor serological cross-reactivity with endemic coronaviruses, IG lots available at the beginning of the pandemic were useless. Plasma manufacturers accordingly initiated manufacturing of freshly manufactured hyperimmune immunoglobulins (HIG) (a.k.a. hyperimmune sera) [2,3], which imply a 10-fold enrichment of IgG levels and loss of IgM and IgA [4]: unfortunately clinical trials largely failed just because they were tested in late COVID-19 stages [5]. Later in the pandemic, COVID-19 convalescent plasma proved to be an effective therapy for IC COVID-19 patients [6], but it is not easy to accommodate for PreEP.

For this reason, both EMA and FDA approved Evusheld™, a cocktail of 2 anti-Spike monoclonal antibodies (tixagevimab and cilgavimab) for PreEP of COVID-19 in IC patients at the beginning of 2022. Unfortunately, recent Omicron sublineages driving pandemic waves have gained complete resistance to Evusheld™ [7], leaving IC patients without any alternative PreEP regimen.

There is generally a 10-month lag between plasma collections and IG lot marketing. As we are now in the middle of year 3 of the COVID-19 pandemic and year 2 of the mass vaccination campaign, there is rationale to believe that the content of anti-Spike antibodies in recently marketed IG batches is increasing [8]. In this systematic review, we show an increasing trend for anti-Spike nAb in IG batches, with titers approaching the ones measured in HIG lots.

On November 18, 2022 we systematically searched PubMed and medRxiv for original research articles published after January 1, 2020 investigating IG formulations for anti-Spike nAb content *in vitro*. We used English language as a restriction for this search. The Medical Subject Heading (MeSH) and key words used were: ("COVID-19″ OR "SARS-CoV-2″ OR "coronavirus disease 2019″) AND ("IVIG" OR "intravenous immunoglobulin" OR "hyperimmune immunoglobulin") AND ("neutralizing antibodies" OR "neutralization"). We also screened the reference lists of the most relevant review and original articles for additional studies not captured in our initial literature search. Supplementary figure 1 reports the PRISMA flow diagram of study selection.

We identified 19 *in vitro* studies, 13 investigating IG and 6 investigating HIG (used as comparators). Most of the studies investigated IG manufactured from collections at the time of wild-type or Alpha VOC, and before the launch of the mass vaccination campaign. Recent IG lots from different manufacturers show nAb titers approaching the ones measured in HIG, which is likely to be ultimate the goal for any IG batch, and reduced inter-lot variability. A single study investigated IG in animal models of COVID-19: Jha et al. further investigated the efficacy of HIG in Syrian hamsters and Ad5-hACE2-transduced mice [9].

A few studies investigated anti-Spike antibodies in the plasma of IC patients after IG infusion. Upasani et al. showed that the median titre increased from 2123 U/ml pre-infusion to 10600 U/ml post-IG infusion in 35 IC patients[10]. Hirsiger et al. conduced a proof-of-concept study in a 34-year-old man with severe antibody deficiency resulting from NFκB insufficiency who had failed to mount humoral anti-SARS-CoV-2 responses after repeated mRNA vaccinations, testing post-infusion plasma nAb levels against Delta and BA.1 [11].

With the vast majority of regular plasma donors across the globe being vaccinated and/or convalescent from previous waves, we have shown here that the time is approaching for IG to become an effective

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Table 1
Summary of *in vitro* studies investigating the neutralizing activity of IVIG batches against SARS-CoV-2.

IG	IVIG product - manufacturer	Period of plasma collection	Dominant SARS-CoV-2 VOC at that time	Serology assay (and target SARS-CoV-2 VOC in the *in vitro* neutralization assay)	*In vitro* activity (mean nAb titer)	Ref.
IVIG/ SCIG	Flebogamma™ (Grifols) Intratect™ (Biotest) Iqymune™ (LFB) Octagam™ (Octapharma) Privigen™ (CSL Behring)	Prior to mid-2022	All VOCs	PRNT Wild-type (USA-WA1) Omicron (BA.1)	ID_{50} varying between 1:25000 and 1:2 × 10^7	[10]
	Gamunex-C™ (Grifols, USA) Flebogamma-C™ (Grifols, Germany)	May 2020- September 2021	Wild type (WA-1, D614G) Alpha (B.1.1.7) Beta (B.1.351) Gamma (P.1) Delta (B.1.617.2)	PRNT Wild-type (USA-WA1) Wild-type (D614G) PRNT Alpha (B.1.1.7) PRNT Beta (B.1.351) PRNT Gamma (P.1) PRNT Delta (B.1.617.2)	Gamunex-C: 422 Flebogamma-C: 875 Gamunex-C: 259 Flebogamma-C: 383 Gamunex-C: 129 Flebogamma-C: 385 Gamunex-C: 117 Flebogamma-C: 139 Gamunex-C: 115 Flebogamma-C: 184 Gamunex-C: 243 Flebogamma-C: 244	[15]
	Gammagard Liquid™ (Baxalta)	March 2020- January 2021	Wild type (WA-1, D614G) Alpha (B.1.1.7) Beta (B.1.351) Gamma (P.1) Delta (B.1.617.2)	PRNT Wild-type (USA-WA1)	Increased from a mean of 1.7 IU/ml by September 2020–31.2 IU/ml by January 2021 (projection to July 2021: ~345 IU/ml).	[16]
	Gamunex™: 5 lots, Iqymune™: 3 lots, Privigen™: 2 lots, Octagam™: 6 lots Hizentra™: 5 lots			Euroimmun ELISA and Abbott CMIA	24/46 samples (52%, CMIA), and 21/38 samples (55%, ELISA) showed relevant IgG reactivity against SARS-CoV-2. Anti-SARS-CoV-2 IgG titers were significantly higher in Gamunex® than in other immunoglobulin preparations in both assays	[17]
	Hizentra™ (CSL Behring)	March 2021 * April 2021 * May 2021 * June 2021 * July 2021 *	Alpha (B.1.1.7)	mNeonGreen fluorescent focus reduction neutralization test against wild-type (USA-WA1)	NT_{50} 41 NT_{50} 109 NT_{50} 193 NT_{50} 759 NT_{50} 2523	[18]
		October 2021 * August 2021 * December 2020 *		Roche Elecsys anti-SARS-CoV-2-Spike-IgG/M assay (no VNT)	39,783 U/ml 12,413 U/ml 29 U/ml	[11]
	Privigen™ (CSL Behring)	April 2021 * May 2021 * April 2021 * March 2021 * July 2020 * September 2020 *	Wild-type		538 U/ml 283 U/ml 158 U/ml 151 U/ml 30 U/ml 17 U/ml	
		April 2021 May 2021		Phadia™ EliA™ SARS-CoV-2-Sp1 IgG assay	250–300 U/ml 700 U/ml	[19]
	3 undisclosed vendors (14 lots)	2019	prepandemic	PRNT Wild type (WA-1), Omicron BA.1, BA.1.1, BA.2, BA.2.12.1, BA.3 and BA.4/BA.5	No neutralizing antibodies against either the ancestral SARS-CoV-2 strain (WA1/2020) or the Omicron sublineages	[20]
	3 undisclosed vendors (14 lots)	2020	Wild type (WA-1, D614G)		11 of the 14 2020 IVIG lots had very low $PsVNA_{50}$ values against WA1/2020 (1:20.7–1:62.1) and no detectable neutralizing antibodies against the 6 Omicron subvariants	
	Gammagard Liquid™ (Baxalta)	September 2020-July 2021	Wild-type (WA-1, D614G) Alpha (B.1.1.7) Beta (B.1.351)	PRNT Wild-type (USA-WA1)	Increased from a mean of 30 IU/ml by January 2021 to > 600 IU/ml by July 2021, with for several lots even higher than those of earlier produced hyperimmune globulin products.	[21]

(*continued on next page*)

Table 1 (*continued*)

IG	IVIG product - manufacturer	Period of plasma collection	Dominant SARS-CoV-2 VOC at that time	Serology assay (and target SARS-CoV-2 VOC in the *in vitro* neutralization assay)	*In vitro* activity (mean nAb titer)	Ref.
			Gamma (P.1) Delta (B.1.617.2)			
	Gammagard Liquid™ (Baxalta), KIOVIG™ (Takeda), Cuvitru SCIG™ (Baxalta)	April 2020-April 2022	All variants	PRNT Wild-type (USA-WA1), Omicron (BA.1)	IVIG lots released in March-April 2022 had a 3–5-fold greater neutralization capacity against wild-type and ~10-fold greater neutralization capacity against Omicron than HIG collected during the early pandemic period (April 2020-October 2020)	[22]
	Octagam™ IVIG (Octapharma), Panzyga™ IVIG, Cutaquig™ SCIF (Octapharma)	December 2020-June 2021	Wild type (WA-1, D614G) Alpha (B.1.1.7) Beta (B.1.351) Gamma (P.1) Delta (B.1.617.2)	PRNT Wild-type (D614G)	Increased a mean of 21 IU/ml in December 2020–506 IU/ml in June 2021 with a maximum of 864 IU/ml for the most recent lots.	[23]
	HyQvia™ (Baxalta Innovations GmbH); Privigen™ (CSL Behring); Intratect™ (Biotest AG); IgVena™ (Kedrion S.p.A); and Flebogamma™ (Grifols S.A.	n.a.	Pre-pandemic	Euroimmun ELISA	9/13 preparations (69.2%), all from 2 different manufactures, were positive (index > 1.1). From one manufacturer, 7/7 lots (100%) and from another 2/3 lots (67%), tested positive. 7/9 of the positive preparations (77%) had titers as seen in asymptomatically infected individuals or recent COVID19-recovered patients, while 2/9 (23%) had higher titers, comparable to those seen in patients with active symptomatic COVID-19 infection (index > 2.2).	[24]
	Flebogamma® DIF and Gamunex®-C	March 2018 to October 2019	Pre-pandemic	PRNT Wild type (WA-1)	For plaque forming unit method, viral neutralization ranged from 79% to 89.5%; PRNT50 titers ranged from 4.5 to > 5. For cytopathic method, viral neutralization ranged from 47% to 64.7%; IC50 was around 1.	[25]
HIG	Universidad de Costa Rica	Prior to September 2021	Wild type (WA-1) Alpha (B.1.1.7) Beta (B.1.351) Gamma (P.1) Delta (B.1.617.2)	PRNT Wild-type (USA-WA1)	Mean ID_{50} VP-IVIG: 0.05 g/L. Mean IC_{50} CP-IVIG: 0.09 g/L	[26]
	COVID-IGIV™ (Emergent BioSolutions Canada, Inc.)	Prior to July 2020	Wild type (WA-1)	PRNT Wild-type (USA-WA1) PRNT Alpha (B.1.1.7) PRNT Beta (B.1.351) PRNT Gamma (P.1) PRNT Delta (B.1.617.2) PRNT Omicron (BA.1)	622 Alliance units (AU)/ml 664 Alliance units (AU)/ml 311 Alliance units (AU)/ml 1069 Alliance units (AU)/ml 192 Alliance units (AU)/ml 106 Alliance units (AU)/ml	[9]
	NPO Microgen JSC (Russia)	April 2020-January 2022	All variants	PRNT Wild-type (WA-1)	Titer 320 (9.4-fold higher than that in the original plasma pool)	[27]
	3 undisclosed vendors (8 lots)	2020	Wild type (WA-1, D614G)	PRNT Wild type (WA-1), Omicron BA.1, BA.1.1, BA.2, BA.2.12.1, BA.3 and BA.4/BA.5	All 8 lots had high neutralization titers against the WA1/2020, ranging between 1:1742 and 1:7303 (GMT of 3319), with cross-neutralizing activity against Omicron subvariants. The neutralization titers against BA.1, BA.1.1, and BA.2 were variable, with 1 lot (hCoV-2IG-7) exhibiting high neutralization titers across all variants (>1:1000), 2 lots had low titers (<1:100) and 5 lots had medium titers (≥1:100 to <1:235). The neutralizing antibody titers against BA.2.12.1, BA.3, and BA.4/BA.5 for all hCoV-2IG lots trended lower, ranging from 1:10–1:753	[20]
	3 undisclosed vendors (7 lots)	2020	Wild type (WA-1, D614G)	PRNT Wild type (WA-1), Omicron (BA.1.1.529)	Titres against WA1/2020 strain, ranging between 1:1118 and 1:3662 (GMT of 2165). A neutralization titer was also observed against Delta and Omicron variants (6/7 lots had neutralization titers against Omicron > 1:117)	[28]
	Chengdu Rongsheng Pharmaceuticals (China)	Mid-2021 (humans vaccinated with BBIBP-CorV)	Wild type (WA-1, D614G)	PRNT Wild type (WA-1, D614G) PRNT Alpha (B.1.1.7) PRNT Beta (B.1.351) PRNT Gamma (P.1) PRNT Delta (B.1.617.2) PRNT Kappa (B.1.617.1) PRNT Omicron (BA.1.1.529)	A broad spectrum, although reduced, neutralization effect against all variants was observed	[29]

Abbreviations: CP, convalescent plasma; HIG, hyperimmune immunoglobulin; ID: inhibitory dilution; IVIG, intravenous immunoglobulin; PRNT, plaque reduction neutralization test; SCIG, subcutaneous immunoglobulin; VP, plasma from vaccinees. *production date.

PreEP strategy also against COVID-19. One of the side benefits of widespread hybrid immunity (vaccination+infection) is the so-called heterologous immunity, *i.e.* cross-reactivity against all sublineages [12].

Even before Evusheld™ totally loose efficacy against Omicron sublineages, the cost-efficacy of the drug (around 2000 USD per patient, with dosing every 6 months thanks to the extended half-life modifications of IgG) had been questioned. IG PreEP potentially offers a strategy at no incremental cost.

Evusheld™ is currently administered intramuscularly (a route preferred to the intravenous one), while IG can be administered monthly either intravenously (IVIG) or subcutaneously (SCIG). SCIG represent a growing trend for the IG market: the formulation being stable at room temperature, it can be administered at home, further reducing the costs and discomfort associated with PreEP. In addition, during the COVID-19 pandemic many hospital-based IVIG patients quickly transitioned to home-based self-administered SCIG[13].

One of the problems with passive immunotherapy-based PreEP is false positivity in serological assays [14]: while this is likely to remain the case also for IG, their shorter half-life (1 month *vs.* 6 months) makes it much easier than for Evusheld™ to identify time windows for serological testing.

Our data clearly show that IG manufacturers should begin to additionally qualify their IG batches for anti-Spike IG content Table 1.

Author contributions

D.F. wrote the first draft, M.F. revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Materials

Supplementary figure 1.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.transci.2023.103648.

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Daniele Focosi[a,*], Massimo Franchini[b]

[a] North-Western Tuscany Blood Bank, Pisa University Hospital, 56100 Pisa, Italy

[b] Division of Hematology and Transfusion Medicine, Carlo Poma Hospital, 46100 Mantua, Italy

[*] Correspondence to: via Paradisa 2, 56124 Pisa, Italy.

E-mail addresses: daniele.focosi@gmail.com (D. Focosi), massimo.franchini@asst-mantova.it (M. Franchini).