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REVIEW

Polyclonal hyper immunoglobulin: A proven treatment and prophylaxis platform for passive immunization to address existing and emerging diseases

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ABSTRACT

Passive immunization with polyclonal hyper immunoglobulin (HIG) therapy represents a proven strategy by transferring immunoglobulins to patients to confer immediate protection against a range of pathogens including infectious agents and toxins. Distinct from active immunization, the protection is passive and the immunoglobulins will clear from the system; therefore, administration of an effective dose must be maintained for prophylaxis or treatment until a natural adaptive immune response is mounted or the pathogen/agent is cleared. The current review provides an overview of this technology, key considerations to address different pathogens, and suggested improvements. The review will reflect on key learnings from development of HIGs in the response to public health threats due to Zika, influenza, and severe acute respiratory syndrome coronavirus 2.

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Introduction

Vaccines represent an active immunization strategy to combat disease, in which the antigen, pathogen, or a fragment of the pathogen is introduced to the host, so that the host's immune system can generate endogenous antibodies in response.[1] Although highly effective, this process may take weeks or months and requires the host to have a non-compromised immune system.[2] In contrast, passive immunization transfers nearly immediate immunity by direct administration of specific antibodies against the pathogen, with intravascular administration being the fastest way to confer protection within hours.[3,4] The specific antibodies may inhibit the pathogen through multiple mechanisms, including binding at epitopes that neutralize by preventing cellular uptake, speeding up clearance, or directed killing through T-cell mechanisms.[5] Passive immunization can be especially important for individuals with a deficient immune system, who do not respond adequately to active immunization.[2] Immunity conferred by passive immunization is generally short-lived (typically weeks to months depending on the antibody source) and dose-related, requiring continued dosing until the infection or toxin has been cleared.[1]

Based on the pathogen and patient population, passive immunization can be an effective treatment option throughout disease progression for prevention of infection for people in high-risk situations, such as frontline healthcare workers and at-risk patients; postexposure prophylaxis; as an early treatment to prevent infected patients from developing severe symptoms; and as a late treatment for people already experiencing severe symptoms. The types of antibodies used in passive immunization can be polyclonal in nature, representing a mixture of antibodies that bind to different epitopes on the pathogen, or monoclonal, representing an antibody that binds a single epitope. The three main types of passive immunization through polyclonal-based immunotherapy include convalescent plasma (CP); intravenous immunoglobulin (IVIG); and, the focus of this review, hyper immunoglobulin (HIG).

Hyper immunoglobulins

HIG therapy is made from plasma derived from donors (humans or animals) with high antibody titers against specific antigenic targets.[6] Thus, HIGs are enriched for a specific target and plasma is pooled from multiple donors to achieve specific and consistent antibody levels that are further concentrated through the manufacturing process. When administered through passive immunization, HIGs are an efficient mechanism to achieve immediate short-term immunization against antigenic targets. They are commonly used in cases of exposure to an infectious disease when no vaccine is available, when a vaccine would not elicit a humoral immune response quickly enough, or when an underlying disease or therapy makes a satisfactory vaccine response unlikely. Furthermore, HIGs can also be used in conjunction with vaccines to confer temporary immunity while waiting for the patient's immune system to respond to vaccination, as in the case of typical rabies treatment.[7]

The advent of HIG development can be traced back to the 1930s when it was discovered that antibodies were localized to the immunoglobulin fraction of human serum. This led to further optimization specifically of fractions containing immunoglobulin G (IgG).[8] The HIG manufacturing technology is

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now well established with multiple licensed products and decades of use in a broad range of populations including vulnerable individuals. Leveraging this history, the platform can enable expedited development and entry into late-stage clinical trials.[9] To support the safe use of HIGs, across multiple patient populations and disease states, regulatory requirements have defined multiple controls on plasma donations as well as validated viral reduction steps within the manufacturing process. First, the donor plasma undergoes screening for a defined panel of pathogens to ensure usability. During the manufacturing process, multiple virus inactivation and removal steps are typically incorporated and validated to provide additional safety controls. Current manufacturing schemes generally consist of either precipitation in solvent according to the Cohn method or a chromatography step for purification with additional steps incorporated for safety including validated viral removal through filtration or chromatography, inactivation via pH, heat, or addition of solvents and detergents, and a reverse-phase chromatography step to remove the solvents and detergents.[10,11] The process often also includes an ultrafiltration step to further concentrate immunoglobulin before it is formulated in preparation for final filtration and filling of the drug product. The final HIG product is, therefore highly purified, with a consistent level of pathogen-specific antibodies per dose.[12] New products developed on the same HIG manufacturing platform can leverage the validated manufacturing controls and assays, as well as supportive information from the safety, pharmacokinetics (PK) and pharmacodynamics (PD) profiles from existing products manufactured on the same platform.

Human HIGs are manufactured from human plasma pooled from donors with specific antibodies to the antigenic target using plasma from either donors who were vaccinated in order to stimulate the production of antibodies (donor-stimulated program)[13,14] or convalescent donors with high measurable titers of desired antibodies.[15–18] Human HIGs represent fully human antibodies with normal diversity and natural glycosylation, and thereby contain inherent properties with an optimal clinical profile (half-life, tolerance, etc). The higher concentration of proteins in HIG products means that a high concentration of antibodies, with a known titer that is consistent batch to batch, can be administered with lower volume and with an established risk-benefit profile across diverse patient populations. In addition, the HIG products using these manufacturing processes result in a formulated final product that supports an extended shelf-life.

The antibodies in HIGs are polyclonal, characterized by high avidity and broad specificity across numerous epitopes and have the potential to bind to different sites of the pathogen, which can impact binding to target receptors, inhibit cellular uptake, and improve clearance. This broad binding activity of polyclonal antibodies may also reduce the likelihood of a pathogen/agent introducing mutations at a targeted site to escape treatment and help exploit vulnerable conserved epitopes or viral clades conferring virulence.[19,20] The precise mechanism of action of HIG therapeutics against infection is multifaceted, but involves at least two aspects: (1) protective antibodies that neutralize specific pathogens/agents and lead to rapid clearance,[21] and (2) ancillary plasma components believed to provide an immunomodulatory effect against infection.[21] Another benefit of polyclonality is the potential for cross-reactivity; for example, CroFab® (Crotalidae polyvalent immune fab [ovine]), an approved HIG indicated for the management of patients with North American crotalid envenomation (includes rattlesnakes, copperheads, and cottonmouths/water moccasins), has been used to treat patients bitten by the hognosed viper (*Pidium nasutum*).[22]

Animal sera have also been successfully used to generate HIG products, especially for pathogens without a vaccine or sufficient human exposure as a plasma source, often the case for emerging infectious diseases or biodefense targets. One key advantage of using an animal system is the ability to use a broader range of vaccines and adjuvants to achieve high-titer antibodies that are needed for treatment in challenging diseases. For example, the treatment of diphtheria in adults requires between 20,000 and 100,000 IU per dose depending on disease severity; however, circulating titers of 0.1 IU/mL in adults offers protective immunity.[23] The low protective titer produced by vaccination makes it infeasible to produce a human HIG with titers for treatment in volumes that would be acceptable. In addition, the animal-derived HIGs can provide a scalable plasma source and more cost-effective treatments. In the past, animal-derived HIGs have resulted in immunogenic reactions and serum sickness;[24–27] however, newer products have incorporated improvements to significantly reduce this occurrence. In most of the US Food and Drug Administration (FDA)–approved products, the Fc portion of the antibodies is removed through enzymatic digestion (e.g. papain or pepsin) to produce antibody fragments consisting of the Fab and $F(ab')_2$ with the antigen-binding sites to reduce immunogenicity. In addition, improvements in the manufacturing process to achieve a higher level of purity than historical animal-derived HIGs have further limited the immunogenicity, as described previously.[27,28] Although the Fc cleavage reduces immunogenicity, the Fab and $F(ab')_2$ antibody fragments have a shorter half-life than a fully intact HIG.[24]

US Food and Drug-Administration–approved products

Currently, there are more than 20 FDA-approved HIGs available on the market (Table 1). They can be separated into four groups: antiviral prophylactics, antitoxin treatments, antivenin treatments, and other therapies. The table may not be a comprehensive list of all currently approved HIG products, and approval may not always translate to availability in the market. The table was compiled from the FDA website for approved immunoglobulins, focusing on HIGs, and the Center for Biologics Evaluation and Research List of Licensed Biological Products. Many more HIGs are approved and available for use in other jurisdictions worldwide but will not be covered in this review.

Antiviral prophylactics

Eight human polyclonal immunoglobulin products are approved for passive immunotherapy against viral infections including varicella zoster (VARIZIG®),[17] rabies (KEDRAB®[13] and HyperRAB®[31]), vaccinia (CNJ-016®),[14] hepatitis A (GamaSTAN S/D®),[32] hepatitis B (HepaGam B®[16] and Nabi-HB®[18]), and cytomegalovirus (CytoGam®).[15] These antiviral HIGs are mostly used

Table 1. Hyper immunoglobulin therapies that are licensed by the FDA.

Group	Proper Name	Origin	Trade Name	Company	FDA Approval	Indication
Antiviral prophylactics						
	Cytomegalovirus immunoglobulin intravenous	Human	CytoGam™	Saol Therapeutics	April 1990	Prophylaxis of cytomegalovirus disease associated with transplantation of kidney, lung, liver, pancreas, and heart
	Hepatitis A immunoglobulin intravenous	Human	GamaSTAN™	Grifols Therapeutics Inc	January 1944	Postexposure prophylaxis for hepatitis A infection Prevention or modification of measles (rubeola) in susceptible persons exposed fewer than 6 days previously Passive immunization in immunocompromised patients to protect against varicella if varicella-zoster immunoglobulin (human) is not available May benefit women who have been exposed to rubella in the first trimester of pregnancy and who will not consider a therapeutic abortion
	Hepatitis B immunoglobulin intravenous	Human	HepaGam B™	Saol Therapeutics	January 2006	Prevention of hepatitis B recurrence following liver transplant in HBsAg-positive liver transplant patients Postexposure prophylaxis including • Acute exposure to HBsAg-positive blood, plasma, or serum (parenteral exposure, direct mucus membrane contact, oral ingestion, etc) • Perinatal exposure of infants born to HBsAg-positive mothers • Sexual exposure to HBsAg-positive persons • Household exposure to persons with acute HBV infection
	Hepatitis B immuneglobulin	Human	Nabi-HB™	ADMA Biologics	March 1999	Treatment of acute exposure to blood containing HBsAg, perinatal exposure of infants born to HBsAg-positive mothers, sexual exposure to HBsAg-positive persons, and household exposure to persons with acute HBV infection in the following settings: • Acute exposure to blood containing HBsAg • Perinatal exposure of infants born to HBsAg-positive mothers • Sexual exposure to HBsAg-positive persons • Household exposure to persons with acute HBV infection
	Hepatitis B immunoglobulin	Human	HyperHEP B™	Grifols	September 1977	Postexposure prophylaxis in the following situations: • Acute exposure to blood containing HBsAg infection • Perinatal exposure of infants born to HBsAg-positive mothers • Sexual exposure to an HBsAg-positive person • Household exposure to persons with acute HBV infection
	Rabies immunoglobulin	Human	KEDRAB™	Kedrion Biopharma	August 2017	Passive, transient postexposure prophylaxis of rabies infection, when given immediately after contact with a rabid or possibly rabid animal and concurrently with a full course of rabies vaccine
	Rabies immunoglobulin	Human	IMOGAM™	Sanofi	April 1984	In conjunction with the standard series of rabies vaccinations, is indicated for individuals suspected of exposure to rabies, particularly severe exposure
	Rabies immunoglobulin	Human	HyperRAB™	Grifols	June 1974	Postexposure prophylaxis, along with rabies vaccine, for all persons suspected of exposure to rabies
	Vaccinia immune globulin intravenous	Human	CNJ-016™	Emergent BioSolutions	May 2005	Treatment of complications due to vaccinia vaccination including: • Eczema vaccinatum • Progressive vaccinia • Severe generalized vaccinia • Vaccinia infections in individuals who have skin conditions • Aberrant infections induced by vaccinia virus (except in cases of isolated keratitis) VIGIV is not indicated for postvaccinial encephalitis.
	Varicella zoster immunoglobulin	Human	VARIZIG™	Saol Therapeutics	December 2012	Postexposure prophylaxis in high-risk groups (immunocompromised children and adults, newborns of mothers with peripartum varicella, premature infants or infants less than 1 year of age, pregnant women, and adults without evidence of immunity)
Antitoxins						
	Anthrax immunoglobulin intravenous	Human	ANTHRASIL™	Emergent BioSolutions	March 2015	Treatment of inhalational anthrax in adult and pediatric patients in combination with appropriate antibacterial drugs

(*Continued*)

Table 1. (Continued).

Group	Proper Name	Origin	Trade Name	Company	FDA Approval	Indication
	Botulism immunoglobulin intravenous	Human	BabyBIG™	California Department of Health Services	October 2003	Treatment of botulism caused by *Clostridium botulinum* (types A or B) in patients below 1 year of age
	Botulism antitoxin heptavalent (A, B, C, D, E, F, G)	Horse	BAT™	Emergent BioSolutions	March 2013	Treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotypes A, B, C, D, E, F, or G in adults and pediatric patients
	Tetanus immunoglobulin	Human	HyperTET™	Grifols	October 1957	Prophylaxis against tetanus following injury in patients whose immunization is incomplete or uncertain Also indicated, although evidence of effectiveness is limited, in the regimen of treatment of active cases of tetanus
Antivenins						
	Antivenin (*Latrodectus mactans*)	Horse	Black widow spider antivenin™	Merck & Co, Inc	1936	Treatment of patients with symptoms due to bites by the black widow spider (*Latrodectus mactans*)
	Antivenin (*Micrurus fulvius*)	Horse	North American coral snake antivenin™	Pfizer	1967	Treatment of envenomation caused by North American coral snakes (*Micrurus*)
	Centruroides (scorpion) immune F(ab')2 injection	Horse	Anascorp™	Rare Disease Therapeutics	August 2011	Treatment for clinical signs of scorpion envenomation
	Crotalidae immune $F(ab')_2$	Horse	ANAVIP™	Rare Disease Therapeutics	May 2015	Management of adult and pediatric patients with North American rattlesnake envenomation
	Crotalidae polyvalent immune Fab	Sheep	CroFab™	BTG International	October 2000	Management of adult and pediatric patients with North American crotalid envenomation (Crotalidae subfamily including rattlesnakes, copperheads and cottonmouths/water moccasins)
Other therapies						
	Antithymocyte globulin	Rabbit	Thymoglobulin™	Sanofi	December 1998	Prophylaxis and treatment of acute rejection in patients receiving a kidney transplant Thymoglobulin is to be used in conjunction with concomitant immunosuppression.
	Antithymocyte globulin, lymphocyte immunoglobulin	Horse	ATGAM™	Pfizer	March 2018	For any patient in whom reduction of peripheral T-lymphocyte function as measured by rosette-forming cell assay could be desirable
	Digoxin immune Fab	Sheep	DigiFab™	BTG International	August 2001	Treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose
	Rho(D) immunoglobulin intravenous	Human	Rhophylac™	CSL Behring	February 2004	Suppression of rhesus (Rh) isoimmunization in • Pregnancy and obstetric conditions in non-sensitized, Rho(D)-negative women with an Rh-incompatible pregnancy, including routine antepartum and postpartum Rh prophylaxis and Rh prophylaxis in cases of obstetric complications, invasive procedures during pregnancy, or obstetric manipulative procedures • Incompatible transfusions in Rho(D)-negative individuals transfused with blood components containing Rho(D)-positive red blood cells
	Rho(D) immunoglobulin intravenous	Human	HyperRHO S/D™	Grifols	June 1971	Full dose: for the prevention of Rh HDN and the prevention of isoimmunization in Rh_O(D)-negative individuals who have been transfused with Rh_O(D)-positive red blood cells Mini dose: prevent the isoimmunization of Rh_O(D)-negative women at the time of spontaneous or induced abortion of up to 12 weeks' gestation provided the following criteria are met: (1) The mother must be Rh_O(D) negative and must not already be sensitized to the Rh_O(D) antigen. (2) The father is not known to be Rh_O(D) negative. (3) Gestation is not more than 12 weeks at termination.

(*Continued*)

Table 1. (Continued).

Group	Proper Name	Origin	Trade Name	Company	FDA Approval	Indication
	Rho(D) immunoglobulin intravenous	Human	RhoGAM and MICRhoGAM™	Kedrion Biopharma Inc.	April 1968	For use in preventing Rh immunization for • Pregnancy and other obstetrical conditions in Rh-negative women unless the father or baby are conclusively Rh-negative, e.g., delivery of an Rh-positive baby irrespective of the ABO groups of the mother and baby, any antepartum fetal-maternal hemorrhage (suspected or proven), actual or threatened pregnancy loss at any stage of gestation and ectopic pregnancy • Prevention of Rh immunization in any Rh-negative person after incompatible transfusion of Rh-positive blood or blood products
	Rho(D) immunoglobulin intravenous	Human	WinRho SDF Liquid™	Saol Therapeutics	March 1995	For use in clinical situations requiring an increase in platelet count to prevent excessive hemorrhage in the treatment of non-splenectomized, Rho(D)-positive • Children with chronic or acute immune thrombocytopenia (ITP) • Adults with chronic ITP • Children and adults with ITP secondary to HIV infection

CMV, cytomegalovirus; FDA, US Food and Drug Administration; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDN, hemolytic disease of the newborn; HIG, hyper immunoglobulin.
Table 1 was compiled from a combination of the FDA website for approved immunoglobulins,[29] with focus on HIGs, and the Center for Biologics Evaluation and Research List of Licensed Biological Products.[30] Indications were sourced from the associated website or product information.

for postexposure prophylaxis; however, CNJ-016® is indicated for the treatment of complications due to vaccinia vaccination.[14]

For many of the viral prophylactics, there are also commercially available vaccines to prevent the disease's occurence. Despite the availability of a vaccine for these diseases, there is still a use case for HIGs in helping to prevent disease progression or complications. For example, VARIZIG® is recommended for postexposure prophylaxis to prevent or attenuate varicella in high-risk individuals including newborns born to pregnant women who develop varicella close to delivery.[17] The use of VARIZIG® in these high-risk newborns was associated with low rates of varicella when administered up to 10 days after exposure.[33–35] Another example is the administration of HepaGam® that has proven efficacy and dose-dependent response in the prevention of hepatitis B virus (HBV) recurrence after liver transplantation.[36] Treatment with this HIG in combination with antivirals further reduces the risk of hepatitis B infection and the need for retransplantation.[36] HepaGam® and Nabi-HB® are also indicated for postexposure prophylaxis after contact with blood or body fluids of serum hepatitis B surface antigen (HBsAg)–positive carriers and in the prevention of mother-to-child (vertical) transmission. For both these viruses, vaccines for the prevention of the disease exist. However, with increasing nonmedical exemption rates and increased globalized travel, the incidence of the disease may increase; therefore, HIGs can play a part in prevention and treatment.

Antitoxins

Four HIGs against toxins are currently approved in the United States, including 3 produced from human plasma (ANTHRASIL® for treatment of anthrax,[37] HyperTET® for treatment of tetanus[38] and BabyBIG® for treatment of infant botulism[39]) and 1 sourced from horses ([BAT®] heptavalent botulism antitoxin[40]). ANTHRASIL® is prepared using plasma collected from healthy, screened donors who were immunized with BioThrax® (anthrax vaccine adsorbed)[41] to achieve high titers of anti-anthrax antibody (meeting minimum potency specifications). HyperTET® is prepared using plasma collected from healthy donors hyperimmunized with tetanus toxoid.[42] BabyBIG® is prepared from the plasma of donors immunized with pentavalent (serotypes A, B, C, D, and E) botulinum toxoid and screened for neutralizing antibodies to type A and type B botulinum toxins. The heptavalent botulism antitoxin, BAT® is a mixture of purified $F(ab')_2$ plus $F(ab')_2$-related immunoglobulin fragments indicated for the treatment of symptomatic botulism following documented or suspected exposure to botulinum neurotoxin serotypes A, B, C, D, E, F, or G in adults and pediatric patients.[43] The production process involves the immunization of horses with a specific serotype of botulism neurotoxin, the purification of each individual serotype, and the combining of serotypes at defined antitoxin titers.

BabyBIG® was initially assessed in a randomized, double-blind, placebo-controlled trial with 129 infants with botulism, treated within 3 days of hospital admission. The trial and postapproval results showed rapid clinical improvement,[44] often associated with significant decreases in duration of ventilation, length of hospital stay, and mean hospital costs per patient.[45] Owing to the unethical or logistically impractical conduct of clinical trials, ANTHRASIL® and BAT® were approved using the animal rule[46,47] to enable licensure of medical countermeasures for "lethal or permanently disabling" conditions.[48] BAT® was well tolerated and provided clinical benefit in treated patients. BAT® administration within 2 days of symptom onset resulted in 100% survival associated with shorter hospital and intensive care unit stays, and shorter duration and need for mechanical ventilation.[49,50] For ANTHRASIL®, clinical data are limited to small, complex patient groups with multiple co-morbidities and different levels of medical support.[51,52] Although vaccinations for tetanus induce the active production of anti-tetanus antibodies, in which protective levels are reported as ≥0.01 U/mL, a recent case study reported the use of HyperTET® in a patient with 800 times the protective level.[53] The incidence of tetanus, botulism, and anthrax poisoning is low, and thus clinical data and reports are sparse. While occurrence is low, and vaccines may be available, widespread vaccination against biothreats (e.g. anthrax) is not standard practice. Therefore in the event of accidental or intentional large exposure events, post-exposure prophylaxis and treatment options are required and therefore these products tend to be stockpiled by governments around the world.

Antivenins

Annually, millions of humans fall victim to animal envenomation, which may result in death or cause permanent disability. The World Health Organization (WHO) estimates that about 5 million snakebites occur annually, resulting in up to 2.7 million envenomations, roughly 100,000 deaths per annum, and approximately 400,000 disabilities.[54] In 2017, the WHO listed snakebite envenomation as a priority neglected tropical disease with a goal to halve the number of deaths and disabilities by 2030 by strengthening the production of antivenoms, improving regulatory control, and rebuilding and reinvigorating the market by ensuring availability, accessibility, and affordability of safe and efficacious products.[54] Products approved by the FDA include ANAVIP®, an antitoxin derived from horses for treatment of North American rattlesnake envenomation; CroFab®, an antitoxin derived from sheep for treatment of North American crotalid envenomation (rattlesnakes, copperheads, and cottonmouths/water moccasins); and the North American coral snake antivenin, derived from horses and indicated for the treatment of envenomation caused by North American coral snakes (*Micrurus*). Although differences exist between products, in general, the antivenin HIGs bind and inactivate venom components, leading to cessation or reversal of the toxic effects of the venom.[55–57]

Spider and scorpion bites also cause envenomation but are not often deadly. Black widow spider envenomation frequently results in severe pain, muscle cramps, abdominal pain, back pain, and hypertension.[58] Antivenin *Latrodectus mactans* is the only antivenom approved in the United States for treatment of black widow spider envenomation. In an evaluation of case studies of symptomatic black widow spider envenomation, the use of this antivenin resulted in three cases that were treated successfully with antivenin *Latrodectus mactans*, showing the safe and effective use of black widow antivenom.[58] Scorpion stings can cause cranial nerve dysfunction, neuromuscular

hyperactivity,[59] and pancreatitis.[60] Anascorp®, an antitoxin derived from horses, is the only FDA-approved HIG for the treatment of scorpion envenomation. The administration of Anascorp® in children and adults was associated with a more rapid resolution of symptoms within 4 hours compared with placebo.[61,62]

Other therapies

Antithymocyte globulin (ATG) is an antibody preparation derived from rabbits or horses hyperimmunized with human thymocytes. It was initially approved for use in the United States as treatment of acute cellular rejection after renal transplantation. Two FDA-approved products are available in the United States: Thymoglobulin® (rabbit-derived plasma) and Atgam® (horse-derived plasma). DigiFab® is a HIG derived from sheep that is indicated for the treatment of patients with life-threatening or potentially life-threatening digoxin toxicity or overdose.

WinRho®, RhoGAM®, and Rhophylac® are human Rh immunoglobulin treatments that are used in the treatment of fetal rhesus incompatibility to prevent Rh immunization, a condition in which an individual with Rh-negative blood develops antibodies after exposure to Rh-positive blood. The administration of Rh immunoglobulin during a second pregnancy is of utmost importance to prevent the onset of fetal anemia (low iron in the blood), miscarriage, stillbirth, or a serious illness in the baby celled hemolytic disease of the newborn.

Passive immunotherapy for infectious disease

One of the many challenges with countering infectious disease threats is the emergence of new strains or the introduction of existing strains to new geographic regions. Both of these can have a devastating impact because of the lack of natural immunity in the general population and the absence of available vaccines and treatments. As knowledge emerges about the specific strain(s), its mechanism of action, and disease sequelae, the timeline to develop therapeutics can be lengthy, affecting the ability to prevent spread and treat individuals who are already infected. The most recent example of this challenge is the current coronavirus outbreak due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged at the end of 2019.

Over the past 30 years, many new infectious diseases have emerged or reemerged (Table 2), causing large numbers of outbreaks, posing significant threats to human health, and having an enormous social and economic impact. With increased travel, expanded urbanization, escalated climate change, and the increasing interaction between humans and animals, the infectious disease landscape and human vulnerability are changing. As a result, the world is experiencing recurrent larger-scale outbreaks and global pandemics, and the trends are likely to continue and intensify in the 21st century. Evidence suggests that approximately 1 new human infectious disease has emerged every 8 months on average; approximately 75% of these emerging infectious diseases (EIDs) were zoonotic in nature, with a majority being viral diseases.[105]

Unfortunately, we are unable to precisely predict and identify future EID risks, leaving the world to face unprecedented challenges with the emergence of infectious diseases like COVID-19, caused by a novel strain of coronavirus with the ability to spread rapidly because no vaccine or treatment is available and no natural immunity exists. Emerging viruses are especially problematic because viral diseases usually have higher transmission rates, cause severe symptoms, and often lead to mortality. Most emerging viral pathogens are RNA viruses, and are characterized by higher mutation rates owing to the lack of proofreading ability of RNA polymerases. Their rapid mutation and adaptation present significant challenges for the development of vaccines and treatments.[106]

It has long been demonstrated that antibody-based passive immunotherapy is an appropriate preventive and therapeutic option to treat infectious diseases. In many viral diseases, HIG is effectively used to mitigate disease severity in postexposure prophylaxis, such as in the treatment for rabies, human cytomegalovirus, varicella zoster virus, and hepatitis B, as indicated in Table 1. Active immunization through vaccination is typically more effective to prevent disease for longer periods and is less expensive than passive immunization with antibody therapy. However, not all individuals respond to vaccination, and effective vaccines have not been successfully developed against many important viral pathogens, especially for newly emerging viral threats.[107] Active immunization often takes a few weeks (or months for vaccines that require >1 dose) for hosts to develop adequate immune protection after vaccination, whereas passive immunotherapy provides immediate protection. This option can be important for individuals with a compromised immune system, including immunocompromised individuals, pregnant women, and geriatric and pediatric populations who may remain vulnerable to infection even if vaccines are broadly available.[108] Conversely, HIGs are a passive immunotherapy produced from a well-established platform technology that can enable expedited development and a favorable safety profile, making it a promising option for the treatment and prevention of emerging viral threats.

Recent multiple EID outbreaks have highlighted the potential of passive immunotherapy as a promising strategy for treating EIDs. Plasma from patients who have recovered from the infection can provide a source of antibodies that recognize a specific target and limit its function, and other plasma components can exert beneficial effects.[109,110] However, there can be significant variability between donors and as a result, individual CP units contain donor-dependent antibody specificities and titers and may carry the risk of inadvertent transmission of bloodborne diseases.[109,110] Because each CP unit offers a limited ratio of donor to patient and requires matched blood types for administration, this individualized treatment is difficult to scale to global levels.[109] In comparison to CP, HIGs are manufactured at a larger scale by pooling plasma from multiple donors to achieve a standardized amount of specific antibodies, allowing a broader range of plasma to be used. Furthermore, HIGs are manufactured to purify and concentrate the IgG component with steps to inactivate and remove viruses for added safety. Both CP and HIG have been used in clinical studies in viral infection outbreaks of filovirus (Ebola and Marburg), arenaviruses (Lassa, Junin), coronavirus

(SARS, MERS, SARS-CoV-2), influenza (H5N1, H7N9, H1N1), and several other outbreaks caused by emerging viral pathogens in the past 30 years (Table 2). While CP is used as an initial response to emerging infections, HIGs tend to be preferred for larger scale and wider spread outbreaks.

IVIG is generally used as prophylaxis to prevent infection from various infectious diseases in patients with primary immune deficiency.[111,112] A key difference among CP, HIG, and IVIG is that IVIG is not enriched for donors with antibodies to a specific disease outside the class label requirements.[113] Clinical case studies have demonstrated that some of the therapeutic benefits of IVIG are conveyed by factors other than neutralizing antibodies (Table 2). Because CP, HIG, and IVIG are closely related, these other factors would also be present in CP and HIG. In viral infections causing hemorrhagic fever (e.g., Ebola hemorrhagic fever and Crimean-Congo hemorrhagic fever), the benefits of nonspecific antibodies and plasma proteins may include preventing excess vascular leakage,[95] treating disseminated intravascular coagulant and severe thrombocytopenia,[83] and restoring the endothelium glycocalyx.[114] Nonspecific polyclonal passive immunotherapy has also been used as a successful anti-inflammatory treatment option in clinical applications, such as IVIG treatment for encephalitis caused by West Nile virus[72,73] and Chikungunya virus.[80]

Another key aspect of antibody-based passive immunotherapy is the polyclonal nature that results from the natural mode of B-cell response diversity. The extraordinarily broad range of binding specificities and diversity of antibodies are achieved through random rearrangement of antibody gene segments and junctional diversity, as well as somatic mutations and affinity maturation following infection or immunization.[115] The resulting complex polyclonal response comprises multiple antibodies binding to multiple epitopes mediating a variety of effector functions, such as complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent cell-mediated cytotoxicity (ADCC).[116] This feature confers broad protection and is less likely to provide selective pressure for viral escape mutants, a significant difference from monoclonal antibody immunotherapy. For example, antibodies from convalescent patients with Chikungunya virus can cross-neutralize other alphaviruses, Mayaro virus and Una virus,[117] and protect against Ross River virus musculoskeletal disease even with limited neutralizing activity.[118] Cross-protection against related viruses provides added potential benefit of developing polyclonal antibody–based passive immunotherapy like HIG to treat viral EIDs.

Hyper immunoglobulins for the treatment of emerging infectious diseases: Key learnings from recent examples

To highlight some key learnings from the development of HIGs to address EID, this section will review recent efforts to address diseases caused by the Zika virus (ZIKV), influenza virus (FLU), and SARS-CoV-2. As HIG development continues, our understanding of passive immunity is expanding and it is critical to apply key learnings across programs to rapidly advance therapeutic solutions to the next EID.

Zika virus

Zika virus was first identified in a sentinel rhesus monkey in 1947 and was isolated from mosquitoes in 1948. It is primarily transmitted through the bite of infected female *Aedes aegypti* and potentially *Aedes albopictus* mosquitoes; however, sexual transmission has also been reported.[119–121] Periodic ZIKV outbreaks have been reported since its identification. In 2007, there was a substantial outbreak on Yap Island, followed by an outbreak in French Polynesia in 2013, and in 2015 ZIKV spread to South and North America. By February 1, 2016, WHO declared ZIKV a public health emergency of international concern.[122] As of July 2019, a total of 87 countries and territories have had evidence of autochthonous mosquito-borne transmission of ZIKV, distributed across 4 of the 6 WHO Regions.[123] The virus may cause mild symptoms including fever, headache, malaise, arthralgia, myalgia, maculopapular rashes, and conjunctivitis,[119] as well as more serious consequences including Guillain-Barré syndrome[124] and other neurological impairments. Infection during pregnancy has been linked to serious adverse fetal and infant outcomes, such as microcephaly,[125] ocular anomalies,[126] intrauterine growth restriction,[127] serious brain anomalies,[128] and other congenital malformations.[129]

The emergence of ZIKV created an urgent unmet medical need to develop interventions that could address emerging endemics or local outbreaks. CP was tested and showed efficacy (Table 2); however, HIG offered several advantages as a sustainable therapeutic option to provide a bridge between the outbreak and vaccine availability and to be administered upon infection to deliver immediate protection. Therefore, development of HIGs was evaluated[100,130–132] for prophylaxis of ZIKV infection in at-risk populations, including women of childbearing potential and pregnant women. ZIKV-HIG, manufactured from human plasma with high titers of anti- ZIKV antibodies, was shown to prevent and/or neutralize ZIKV infection in preclinical studies using an immune-deficient mouse model (*Ifnar1*$^{-/-}$). The dose-dependent efficacy of ZIKV-HIG in comparison to vehicle control in both pre- (1 h before exposure) and postexposure (24 hours after exposure) settings was established in this highly robust animal model.[100] ZIKV-HIG preclinical efficacy data are consistent with the notion that the neutralizing antibody levels confer protection from ZIKV infection, supported by both animal studies and clinical findings.[101,133] Similarly, ZIKV-HIG manufactured from plasma from transgenic cattle with anti-ZIKV antibodies was shown to be effective in *Ifnar1*$^{-/-}$ mice when treated 1 or 3 days after challenge; no ZIKV-induced tissue damage was evident in the brain and testes and there was protection against testicular atrophy.[130] Furthermore, studies have also shown that neutralizing antibodies prevent ZIKV vertical transmission during pregnancy in nonhuman primate and murine models.[134,135]

Because of the severe outcomes of ZIKV infection during pregnancy, immunotherapy to prevent transmission to the fetus would provide the most clinical benefit. Transplacental transfer of IgG during pregnancy provides passive immunity to the fetus and is critical to protecting newborns against infections and immunological diseases.[136] For example, administration of

cytomegalovirus-specific HIG to pregnant women with primary cytomegalovirus infection significantly reduced the rate of intrauterine transmission from 40% to 16%[137]; hepatitis A and hepatitis B (HBV) immunoglobulins are medically necessary to prevent the mother-to-child transmission of hepatitis viral infections[138]; and WinRho anti-D HIG has been routinely given to Rh-negative women and shown in both clinical trials and postmarketing surveillance to be safe and effective in the treatment of idiopathic thrombocytopenic purpura and in the prevention of Rh isoimmunization.[139]

Pregnant women are considered a vulnerable population with a high bar for therapeutic development to ensure safety and positive risk-benefit ratios. Hyper immunoglobulin products have well-established and robust safety profiles in pregnant and pediatric populations, supported by multiple clinical studies of the effectiveness, safety, and benefits of HIG therapy for pregnant women in diverse settings and by FDA-approved HIG products (Table 1). A stepwise approach for the clinical evaluation of ZIKV-HIG is required before studying the benefits for pregnant women, with initial safety being established in a phase 1 study in normal healthy volunteers.

Another key safety consideration for ZIKV-HIG development is the potential of ZIKV-HIG to cause antibody-dependent enhancement (ADE), so additional evaluation of cross-reactivity and ADE of ZIKV and dengue virus (DENV) infection was completed in *in vitro* and *in vivo* systems (unpublished data). Antibody-dependent enhancement has previously been described for DENV, and during the ADE process, preexisting non-neutralizing or subneutralizing antibodies that recognize one serotype of DENV enhance subsequent different serotypes of DENV infection and pathogenesis.[140] ZIKV and DENV are genetically and antigenically similar (~56% amino acid identity[141]), and cross-reactivities between them have been documented extensively.[142,143] The cross-reactive antibodies have been demonstrated to have the capacity to both potentiate disease and mediate protection during flavivirus infection.[143] To define the boundary of therapeutic efficacy and potential for ADE, ZIKV-HIG was shown to contain cross-reactive neutralizing and enhancing antibodies to DENV, with the potential to enhance ZIKV and DENV disease in an immune-deficient mouse model (unpublished data). However, evidence obtained in nonhuman primates and human cohorts established no correlation to ADE when ZIKV infection occurred in the presence of preexisting DENV immunity.[144,145] Moreover, observations from arbovirus surveillance in Brazil suggest a decrease in DENV circulation after the ZIKV outbreak, possibly due to DENV cross-neutralization by ZIKV antibodies.[146] More targeted studies are required to collect clinical and seroepidemiological surveillance data to establish whether ADE risk is present after passive administration of anti-ZIKV antibodies. The limitations of *in vitro* and *in vivo* models for evaluation of ADE for immunotherapy needs to be considered for HIG development for EID targets.

Influenza

Seasonal influenza remains a significant global public health burden and causes roughly a billion cases of respiratory illnesses per year, approximately 3 to 5 million of which are severe, and between 290,000 and 650,000 annual deaths worldwide despite vaccine and antiviral drug development efforts.[147,148] Generally, influenza A (H1N1, H3N2) or B viruses cause mild or moderate respiratory infections, but they can also trigger serious complications such as pneumonia, secondary bacterial infections, respiratory failure, and death in the very young, geriatric, immunocompromised and other high-risk populations.[149] Although neuraminidase (NA) inhibitors can be used to treat uncomplicated influenza when administered within the first 48 hours of onset of symptoms,[150] there are no FDA-approved therapies for severe influenza in hospitalized patients. Because antibodies play a key role in reducing the severity of influenza infection,[151] passive immunotherapy can be a potential strategy to treat influenza virus infection, modify the outcomes of severe disease, and provide additional benefit to the standard of care; however, the ability of a polyclonal immunotherapy to address the complexity of different influenza strains and cross-neutralization potential needs to be evaluated.

The antibody response to influenza virus infection is multifaceted and complex. On one hand, the majority of antibodies induced by immunodominant antigens hemagglutinin (HA) and NA recognize only the homologous antigenic subtype, so that the seasonal vaccine must be adjusted annually to reflect the specific antigenic drift. On the other hand, cross-reactive and broad neutralizing antibodies have been discovered that recognize the stalk domain of HA,[152] conserved epitopes in the head domains of HA and NA[153,154], and the ectodomain of M2.[155] For the development of an influenza HIG (FLU-HIG), the potency of the product should be aligned with the seasonal vaccine strains recommended by WHO. There are a few items for consideration as it relates to this approach. Firstly, in the event that there is a mismatch of the circulating strain compared to the WHO vaccine recommendations, the potency of the product may not translate to clinical efficacy, so the potency assays for FLU-HIG may need to be adapted to these circulating strains to accurately identify the protective antibodies and predict clinical efficacy. Secondly, hemagglutination inhibition (HAI) or microneutralization assays measure neutralization of HA; however, the non-neutralizing, non-HA, or broadly cross-reactive antibodies may not be identified by these routine assays although they may contribute to efficacy and the protection may be dependent on effector function.[156,157]

The potential for antibody-based passive immunotherapy to improve outcomes of influenza infection for seasonal and pandemic strains has been evaluated in nonclinical and clinical studies[158] with several HIG products from different sources including human, horse, and humanized cow plasma.[159–162] Animal models used for the study of influenza viruses and therapies (including antivirals and vaccines) include mouse and ferret models. The ferret model is the gold standard because ferrets share similar lung physiology with humans, display human characteristics of influenza disease, and respond to human vaccines. In addition, the ferret model is well suited for studying both the pathogenicity and transmissibility of human and avian influenza viruses.[163] FLU-HIG from human plasma was effective against H1N1 infection in a lethal mouse model and reduced lung viremia in a ferret infection model; however, in ferrets, there was no reduction of viral load in a nasal wash.[162] A limitation of the ferret model is the rapid

systemic clearance of human IgG (~14 h h by HAI assay) and limited bioavailability at the nasal passages.[162] The finding of a substantially shorter half-life of human IgG in ferrets compared with humans highlighted the importance of interpreting the animal data used for HIG development within the context of specific species-biomolecules interaction.

The clinical benefit of different preparations of FLU-HIG derived from human plasma has been evaluated in several randomized controlled trials; however, the studies have been inconclusive. Some studies showed that the treatment of severe influenza infection with a FLU-HIG was associated with a lower viral load and reduced mortality,[86,164] but a phase 3 trial using FLU-HIG–containing anti-influenza A and B antibodies was not able to demonstrate a significant clinical benefit for hospitalized patients, although data supported improvement for patients with influenza B.[165] Another phase 2 study with a different FLU-HIG to evaluate a high and low dose of FLU-HIG (NCT03315104) was completed in 2019; the outcome of the study has not yet been published. Further understanding of how these FLU-HIG products differed in potency from the specific strains and dose is still needed. Multiple factors contribute to particular outcomes of a clinical trial and may account for the discrepancy observed in different trials. A few possible explanations for the differences between studies have been suggested, including how titers are measured (conventional HAI titers to assign potency may not be the appropriate surrogate for an effective humoral response in therapeutic studies), the potential for a disconnect in how well antibody affinity correlates with protection or neutralizing capacity, and what titers are required to treat versus prevent infection (treatment is likely to require much higher concentration of antibodies than that required for the correlate of immunity i.e. 1:40 or 1:80 titer).[166] Further analysis of the role of neutralizing potency, the time to intervention, the ideal patient populations, and clinical outcomes, including use of an ordinal scale, are needed.

COVID-19

The COVID-19 pandemic has affected millions of patients worldwide. As of December 1, there have been more than 63 million cases reported globally and more than 1.4 million deaths reported since its detection in early 2020.[167] The COVID-19 pandemic has spread to more than 220 countries, demonstrating that globalization has increased the threat of EIDs.

There is an urgent need for therapeutic options to treat severe cases, prevent the progression of mild-moderate disease to severe disease and stop the spread of the virus. We know from our experience with influenza that even when a vaccine is available, vaccination rates vary and may not protect specific populations from infection, hospitalization, or mortality. Early in the outbreak, the strategy to rapidly develop a HIG product (COVID-HIG) from human plasma with SARS-CoV-2 antibodies was advanced by multiple companies.[168] As a therapeutic, the goal of COVID-HIG administration is to augment the humoral immune response to COVID-19 infection, potentially enhancing viral neutralization and clearance and limiting disease progression and viral replication that can lead to extensive tissue damage and inflammatory responses in the lungs and other organs before the host is able to develop neutralizing antibodies.[169] Based on the established use of several licensed HIG products as a prophylactic treatment for other viral diseases (Table 1), COVID-HIG may also be effective as a postexposure prophylaxis to deliver passive immunity to high-risk populations, such as the geriatric, immunocompromised patients, and frontline healthcare workers.

In developing a COVID-HIG, it is essential to understand SARS-CoV-2 and the associated immune response. The use of CP helps build our understanding of the immune response and the requirements for COVID-19 therapy, yielding information about the required titer of neutralizing antibodies for an intervention, the timing of the intervention, and the impact of the antibody therapy. The availability of CP enables its use as a treatment early in an outbreak because it requires no processing and is available immediately after collection, and as such, case studies and controlled trials using CP were reported throughout the current COVID-19 pandemic. Some studies demonstrated reductions of mortality, increases in respiratory function, and decreases in inflammatory indices,[102,170–172] whereas others showed no difference between CP and placebo.[173] A key difference among these studies was the anti-SARS-CoV-2 antibody titer and subclass contained in the CP used; these factors vary greatly depending on the individual and the time of collection post-recovery.[174]

On August 23, 2020, the FDA issued an emergency-use authorization for COVID-19 CP to treat hospitalized patients.[109,175] However, they noted that well-controlled randomized clinical trials were still necessary to establish efficacy and determine the optimal product attributes and appropriate patient populations for treatment.[176] Currently, the National Institutes of Health and other organizations are expanding study enrollment in randomized controlled studies to further evaluate CP as a treatment for patients hospitalized with COVID-19.[175] The limitations for ongoing use of CP are the lack of consistency in specific antibodies in each dose, blood type-matching requirements and complexity of regulatory oversight because it is not a standardized product with regulatory approval,[177] and transition to HIG in the treatment paradigm for COVID-19 is a logical next step.

An efficacious COVID-HIG dose needs to be determined based on a standardized level of neutralizing antibodies, although the polyclonality will include antibodies that are non-neutralizing and may add to efficacy of the treatment. The putative binding site of the neutralizing antibody target is not well defined; researchers have reported binding to the receptor-binding domain (RBD),[178] the S1 domain of the trimer spike protein,[179] and the full-length trimer spike protein.[180] CP studies thus far have reported highly variable results regarding levels of antibodies against the three different antigens (RBD, S1 domain, and full-length spike protein).

The ability to manufacture COVID-HIG requires a sufficient source of plasma with antibodies to SARS-CoV-2. As we learn about SARS-CoV-2 over time, questions arise regarding the robustness, functionality, and durability of the antibody response as well as the sustainability of the response upon virus reexposure. The antibody response varies across patient populations; a recent study by Mount Sinai showed that

Table 2. Polyclonal passive immunotherapy against emerging and/or zoonotic viral diseases in the past 30 years.

Infectious Agent	Major Outbreaks	Cases/Mortality/Clinical Impact	Treatment	Clinical Findings Regarding Polyclonal Passive Immunotherapy	References
JUNV	Until 1992	Argentine hemorrhagic fever with 20%–30% mortality	CP: clinical trial	CP showed efficacy, reduced mortality to 1%; current SOC	63
SNV/ANDV	1993, 2012, 2017,2019	Hantavirus cardiopulmonary syndrome with 30%–50% mortality	CP: nonrandomized trial Immune sera: preclinical efficacy	CP reduced case fatality rate from 32% to 14%	64–66
EV71	1997–2004, 2008, 2013	Cardiopulmonary or neurological complications and mortality in severe cases	HIG	N/A (Preclinical efficacy has been demonstrated)	67
H5N1	1997, 2003, 2013	~60% mortality	CP: clinical application HIG: preclinical efficacy	CP case studies: significantly reduced viral load and patients survived	68–70
MARV	1998, 2004, 2012	~50% mortality	Polyclonal IgG	Postexposure IgG treatment was protective, with no signs of disease or detectable viremia in NHP	71
WNV	1999–2018	About 1 in 150 develop serious/ fatal illness; neurological WNV has 5%–14% mortality	HIG, IVIG	HIG and IVIG case studies: early administration associated with recovery of neurological features; phase 1/2 trial: no significant difference in outcomes	72–74
LASV	2000	~100,000–300,000 cases annually; ~5000 deaths	CP: clinical application	CP: treated 47 patients; early administration showed rapid improvement of symptoms	75
NiV	2001, 2007, 2018	40%–60% mortality	Polyclonal antibody	N/A (Preclinical efficacy has been demonstrated in hamsters)	76
SARS	2003	8096 people in 29 countries got SARS and 774 died in 2003	CP: clinical application HIG	CP: early treatment was beneficial, significantly reduced fatality rate	77–79
CHIKV	2004–2005, 2007, 2010, 2013–2020	>2 million cases worldwide	HIG, IVIG	HIG: nonrandomized phase 1/2 trial in high-risk neonates born to CHIKV-viremic mothers IVIG: clinical application for CHIKV encephalitis	80–82
CCHFV	2008–2010, 2013–2016	3%–30% mortality	HIG, IVIG: clinical studies	HIG: reduced viral load and improved survival rate in high-risk patients Fresh frozen plasma and IVIG: to treat disseminated intravascular coagulation and severe thrombocytopenia	83–85
H1N1	2009	151,700–575,500 deaths worldwide during the first year the virus circulated	CP and IVIG: clinical application HIG: clinical trial	CP: significantly reduced fatality rate HIG: treatment within 5 d of onset associated with lower viral load and reduced mortality	86–89
DENV	2010, 2012, 2016, 2017, 2019	~390 million per year	HIG	HIG: demonstrated broad neutralizing activity against different serotypes	90
MERS	2012	~35% mortality	CP: case study HIG: clinical trials	CP: decrease the viral burden HIG (from transchromosomic cattle): double-blind, placebo-controlled phase 1 trial	91–93
H7N9	2013	~30% mortality	CP: case study	CP: clinical improvement and recovery of a patient not responding to oseltamivir	94
EBV	2013–2014, 2018–2020	~50% mortality	CP: clinical study HIG	CP: no clear evidence for the prevention of deaths HIG: N/A (preclinical efficacy has been demonstrated in NHP)	95–99
ZIKV	2015	5%–14% of children from infected mothers had congenital Zika syndrome	CP, HIG	CP: preclinical efficacy in NHP HIG: preclinical efficacy and phase 1 clinical trial	100,101
SARS-CoV-2	2019–present	Ongoing pandemic	CP, HIG	CP: clinical trial ongoing HIG: clinical trial ongoing	102–104

CCHFV, Crimean-Congo hemorrhagic fever virus; CHIKV, Chikungunya virus; CP, convalescent plasma; DENV, Dengue virus; EBV, Ebola virus; HIG, hyper immunoglobulin; IgG, immunoglobulin G; IVIG, intravenous immunoglobulin; JUNV, Junin virus; LASV, Lassa virus; MARV, Marburg virus; NHP, nonhuman primates; NiV, Nipah virus; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SNV/ANDV, Sin Nombre virus/Andes virus; SOC, standard of care; WNV, West Nile virus; ZIKV, Zika virus.

although the majority of COVID-19–positive individuals had moderate to high titers of anti-spike antibodies,[181] asymptomatic or mild cases resulted in lower antibody production compared with moderate or severe cases.[182] In this study, convalescent patients were also determined to have higher antibody levels than inpatients, which supports a positive correlation between recovery and days since onset of the virus.[182] Many factors have been suggested to have an effect on antibody levels, including sex, older age, ABO blood type, and hospitalization,[183] but more comprehensive data sets are required to confirm any associations. The challenge for manufacture of a COVID-HIG product is accessing sufficient

quantities of plasma with necessary levels of IgG antibodies to neutralize SARS-CoV-2; current efforts have suggested that approximately 55% of known convalescent patients are suitable donors (unpublished results). As COVID-19 vaccines become available, plasma from vaccinated donors may provide a more consistent source of plasma for COVID-HIG.

Like other RNA viruses, SARS-CoV-2 mutates frequently, resulting in enhanced virulence and evolution, which are requirements for the virus to survive.[184] The neutralizing effects of COVID-19 treatments including monoclonal or polyclonal antibodies could be affected as the virus mutates over time, particularly with mutations that have occurred in the RBD. In genomic studies from SARS-CoV-2 isolates worldwide, single-point mutations were compared and segregated into six clusters worldwide, with four of them prominent in the United States.[185,186] SARS-CoV-2 mutations thus far have occurred in the absence of strong positive selection pressure caused by natural immunity or other interventions, but is predicted to change under the selective pressure of widely deployed neutralizing antibody prophylactics.[187] The virus may rapidly become resistant to single monoclonal antibodies; hence, combinations of 2 to 3 neutralizing antibodies or polyclonals for effective prophylaxis or treatment of COVID-19 have therefore been suggested.[187] One point mutation in the spike protein (D614G) has occurred such that the G614 variant is now more commonly isolated than the original D614 variant. *In vitro* and animal studies have indicated that the G614 variant may have increased infectivity, and may be associated with higher viral loads and more severe infections. However, antibodies induced against the D614 variant were found to cross-neutralize against the G614 variant.[188,189] Furthermore, antibodies in CP from New York City reacted to both D614 and G614 variants.[190] Another point mutation, the N439K on the RBD, enables the virus to bind the human ACE2 receptor with higher affinity than the original variant. The antibodies in convalescent sera from 439 recovered individuals displayed lower potential for binding to the RBD of the K439 variant versus the N439 variant;[191] whereas antibodies isolated from convalescent sera from 6 individuals who recovered from infection with SARS-CoV-2 N439K showed no difference in binding affinity between the 2 variants.[191] These findings reiterate the importance of the polyclonality and heterogeneity offered by HIGs in the fight against multiple strains of SARS-CoV-2 when considering point mutations due to selective pressure and widespread exposure.

In addition to the COVID-HIG products derived from human plasma, several products derived from horse plasma have been advanced. Caja Costarricense de Seguro Social (Costa Rica, NCT04610502),[192] Hospital San Jose Tec de Monterrey (Mexico, NCT04514302),[193] and D'Or Institute for Research and Education (Brazil, NCT04573855)[194] all have Phase 1/2 trials at various stages, and Inmunova Inc (Argentina, NCT04494984)[195] has a Phase 2/3 trial estimated to complete in December 2020. SAb Biotherapeutics has also initiated 2 Phase 1 clinical trials for COVID-HIG (SAB-185) manufactured from plasma using transgenic cattle expressing human immunoglobulin G.[196,197] Data from these trials are anticipated to further contribute to knowledge on the immune response, potency requirements and efficacy of HIG products.

Future directions

As indicated above, the antibody response to viral or pathogenic infections in humans may be highly variable. One exploratory route to alleviate the need for human plasma includes the humanization of various animals (e.g., cows, pigs) to yield antibodies similar or equivalent to those produced by humans. As mentioned above, SAb Biotherapeutics has developed transgenic cattle engineered to possess a human artificial chromosome containing the human antibody heavy chain and kappa chain.[198,199] The transgenic cattle platform has been used to develop HIGs against various viral pathogens including ZIKV,[131] Ebola virus,[200,201] Middle East respiratory syndrome coronavirus,[91,202] seasonal influenza virus,[203] and SARS-CoV-2.[204] HIGs produced using this technology are being evaluated in clinical trials. As another humanization strategy, Xenothera (France) has engineered animals lacking specific enzymes so that the animals produce glycohumanized polyclonal antibodies.[205] This technology was originally developed for xenotransplantation purposes, but the glycohumanized polyclonal antibodies derived from these animals have been clinically shown to confer immunosuppression in kidney transplant recipients in a first-in-human study (NCT04431219).[206] XAV-19, a glycohumanized polyclonal antibody against SARS-CoV-2, is currently being investigated in a phase 2 clinical trial (NCT04453384).[207]

As another strategy for HIG development, companies such as GigaGen and Symphogen have developed single-cell antibody discovery and development platforms to create recombinant polyclonal immunoglobulins. The process involves isolating and characterizing B cells from infectious disease patients to identify neutralizing antibodies and manufacturing polyclonal antibodies using a recombinant approach. Products based on this approach are in early development; they include Sym002 (smallpox (vaccinia) antibodies),[208] GIGA-2050 (recombinant anti-coronavirus immunoglobulin),[209,210] and recombinant IVIG.[211]

Furthermore, the mode of antibody administration is another avenue to explore. Generally, antibodies are administered via intravenous, subcutaneous, or intramuscular routes depending on the dose volume; however, companies are exploring administration directly to airways either by nebulization or aerosol delivery.[212–214] This mode of administration may be particularly beneficial for respiratory pathogens, such as COVID-19; direct antibody deposition in the airway would bind to and neutralize SARS-CoV-2 virus particles and may enable a higher efficacy with a lower dose in inhibiting infections in the lung.[215–217] This technology is being evaluated for antibody therapeutics including monoclonals,[218–222] other modalities (nanobodies,[223–225] IgY[226,227]), and possibly HIGs.[216]

Concluding remarks

Passive immunization remains an important treatment modality to provide the immediate benefit of protective antibody levels. For passive immunization with polyclonal therapies, the antibody source can be human or animal plasma. One of the most well-established and proven platforms for passive immunization is HIG, with more than 20 FDA-approved products to address a broad range of targets or pathogens. The ability to

leverage these HIG platforms to expedite development of new products to address EIDs has been demonstrated, and the polyclonal nature of HIG offers advantages regarding strain heterogeneity and the potential for cross-neutralization. In addition, the well-defined safety profile of HIG is an important benefit particularly in vulnerable populations, such as geriatric, pediatric, pregnant, and immunocompromised individuals, who are often the most affected by EIDs. HIGs can be an effective treatment option throughout disease progression (pre-exposure, postexposure prophylaxis, early treatment to prevent severe symptoms; and late treatment for patients experiencing severe symptoms). Some common challenges remain, including defining a consistent, reliable, and scalable source of antibodies and determining the potency of the antibodies specific for each disease state. Overall, the key learnings from the many approved HIG products and candidates in development to address EID can provide a template for future response and a critical tool to address new and emerging threats.

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