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THE USE OF CONVALESCENT PLASMA AS A NOVEL TREATMENT IN PANDEMIC DISEASE: A REVIEW

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ABSTRACT

At present, antibody-based therapies are undergoing a renaissance. In the wake of being created and afterward to a great extent relinquished in the twentieth century, many antibody preparations are presently in clinical use. Interest in utilizing antibodies to treat irresistible infections is now being fuelled by the wide dissemination of drug-resistant pathogens, the rise of new pathogens, the overall inefficacy of medications in immunocompromised hosts and the fact that antibody-based treatments are the main way to give prompt resistance against biological weapons. Given the requirement for new drug therapies and numerous ongoing innovative advances in the field of immunoglobulin research, there is generous affirmation concerning improved applications of antibody- based therapy for the anticipation and treatment of infectious diseases. The advent of new pathogens for which there is no compelling treatment alternative has redrawn the regard for the usefulness of convalescent plasma. To be sure, convalescent plasma can be an alternate and quick remedial choice in outbreaks of infectious diseases such as Middle East Respiratory Syndrome, Severe Acute Respiratory Syndrome (SARS), H1N1 flu, H5N1 flu , Ebola, Poleomyelitis, Measles and COVID-19.

INTRODUCTION

Passive antibody therapy: Passive antibody therapy was the essential reliably viable antimicrobial strategy. The ability of specific antibodies to protect against bacterial toxins was discovered by Behring and Kitasato in the mid 1890s, and this perception prompted to the rapid advancement of antibody therapy for the treatment of different irresistible infections. As all antibody preparations were derived from the serum of immunized animals or immune human donors, this type of treatment was known as 'serum therapy". Serum treatment was successful; nevertheless the administration of tremendous amounts of animal proteins was typically accompanied with side effects that extended from immediate hypersensitivity reactions to serum sickness, which is a type of antigen–antibody complex disease [1]. By the 1930s, enhancements in antibody refinement strategies allowed the production of antibody preparations with reduced toxicity, in this way serum therapy was an effective methods for treating numerous irresistible infections. Be that as it may, after 1935, the use of serum treatment declined quickly because of the introduction of sulphonamides and, shortly thereupon, various classifications of antimicrobial chemotherapy. By the late 1940s, serum was largely abandoned as an antibacterialagent, however

antibody agent based therapy held a niche as a treatment for venoms, toxins and certain viral infections[2]. However, in the half of the twentieth century, the deficiency to treat certain viral infections drove endeavors to create antibody preparations derived from immunized human donors for the prophylaxis and treatment of rabies, hepatitis A and B, varicella–zoster virus and pneumonia brought about by respiratory syncytial virus (RSV). A general standard of passive antibody therapy is that it is more effective when utilized for prophylaxis contrasted with treatment of disease. At the point when utilized for therapy, antibody is most effective when administered soon after the onset of symptoms. The purposefor temporal variation in efficacyis notwell understood however could reflect that passive antibody works by neutralizing the initial inoculum, which is probably going to be a much smaller than that of established ailment [3]. Another clarification is that antibody works by modifying the inflammatory response, which is likewise more effectively accomplished during the underlying immune response, a phase that might be asymptomatic [4]. For instance, passive antibody therapy for pneumococcal pneumonia was best when administered shortly after the onset of symptoms, and there was no advantage if antibody administration was postponed past the third day of infection [5]. For passive antibody therapy to be effective, an adequate measure of antibody must be administered. When given to a susceptible individual, this antibody will circulate in theblood, reach tissues, and provide protection against infection. Contingent upon the antibody amount and composition, the protection bestowed by the transferred immunoglobulin can last from weeks to months. The purpose of this review is to discuss the use of convalescent plasma as an alternate choice for the treatment of infectious diseases such as Middle East Respiratory Syndrome, Severe Acute Respiratory Syndrome (SARS), H1N1 flu, H5N1 flu , Ebola, Poleomyelitis, Measles and COVID-19 .

HISTORICAL PERSPECTIVE:

It is noteworthy that historically, convalescent sera were developed and used in many cases without the means to measure antibody titers or knowledge about viral serotypes, and in clinicalstudies that did not meet modern standards for randomization or blinding.The use of convalescent plasma is not new; it was used for severe acute respiratory syndrome (SARS), pandemic 2009 influenza A (H1N1), avian influenza A (H5N1), several hemorrhagic fevers such as Ebola, and other viral infections. This knowledge was converted into human usein 1916, when 26 patients with acute poliomyelitis were treated with convalescent serum from polio survivors with some favourable outcomes [6]. Subsequently, convalescent serum was used to treat many infectious diseases including influenza, as well as prophylaxis against measles[7,8].

Dating back to 1916, a report was published by Harlod L, Amos which depicted about the technique used and the outcomes accomplished in twenty-six instances of acute poliomyelitis in New York treated with human serum acquired from recovered patients. The perceptions followed by Flexner and Lewis, 1909 discovered the recuperation of poliomyelitis patients by the detection of immunity or neutralizing substances in the blood serum. They endeavored to prevent the development of infection in inoculated monkeys through the administration of blood serum taken from (a) recovered monkeys and (b) from recovered human beings. The method was first to make an intracerebral inoculation of the active adapted monkey virus , and then about 24 hours later , to begin treatment by intraspinal injection of immune serum.Later on , Netter and his associates have revealed an aggregate of thirty four cases of acute polymyeletis which they have treated by subdural method of injecting immune serum. By carrying out this they have undoubtedly established the fact that it is considered to be safe in man as in the monkey[6,7].

The animal serums accessiblewere those of Tunnicliff, Degkwitz, and Ferry and Fisher. All these were prepared from a green streptococcus, the causative agent of the disease. In a comparative survey of these serums with convalescent serum, Gunn of the Metropolitan Asylums Board decisively demonstrated that human serum was by far the most reliable.In 1931, Nabarro DN reported the use of convalescent plasma as prophylaxis of measles. As the measles occurs mostly in children, it was difficult to acquire adequate sample therefore

blood samples were taken from adults to treat the infection[9,10].Between the seventh and fourteenth days after defervescence200 to 300 ccm.of blood was collected aseptically into sterile oxalate solution, this permitting a yield of 50 percent of serum after precipitating the oxalate with calcium chloride. Sterility tests and a Wassermann reaction were done on every serum and, after having satisfactory results , 0.5 percent phenol was added and the serum wasthen pooled with several other serums so as to obtain as far as possible a final product of uniform potency. In order to achieve complete protection the serum should be injected before the fifth or sixth day of incubation. This was alludedas"sero-prevention", and results in a passive immunity which lasts roughly a month.They recommended convalescent measles serum as the only weapon for preventing measles, and it ought to be more widely used than it is at present[11].

The outcomes of patientswho received convalescent plasma in Hong Kong during the 2003 SARS outbreak was reported by Cheng et al., 2005. In spite of the fact that this investigation was not a randomized trial, of 1775 patients, the 80 who received convalescent plasma had a lower mortality rate (12.5%) compared with the overall SARS-related mortality for admitted patients (n = 299 [17%]). The antibody titers and plasma transfusion volumes varied and did not seem to correspond with clinical response; however, patients receiving transfusion within 14 days of symptom onset (n = 33) had better outcomes. No adverse events were reported among patients receiving convalescent plasma[12].

Hung IF, et al., 2009 detailed the decrease in mortality rate by the use of convalescent plasma in patients with severe pandemic Influenza A (H1N1) virus infection[13].Themajority of patients infected by pandemic influenza A(H1N1) 2009 virus had a mild illness, severe diseases and mortality occurred in those with extremes of age, immunosuppression, obesity, pregnancy, and other underlying illnesses.Regardless of the use of double-dose oseltamivir and inhaledzanamivir, patients with severe illness had delayed clearance of viral load in respiratory secretions, associated with relentless elevation of cytokines in their serum samples. In this manner, there was an urgent need to find alternative therapeutic regimensfor managing this subgroup of patients. Robust protection from lethality for at least 72 h after infection was demonstrated for monoclonal antibodies with neutralizing activity produced by immortalized B lymphocytes of convalescent patients recovering from influenza A(H5N1) virus infection in a murine model challenged by the hypervirulent influenza A(H5N1) virus[14] .Meta-analysis on contemplates using convalescent bloodproducts in the 1918 influenza pandemic suggested that such a methodology could reduced the mortality rate of severe cases by .50% [15]. Therefore, an imminentmulticenter case-control study was conducted. The findings suggested that 1 dose of convalescent plasma with NAT of >1:160 was effective in reducing mortality, respiratory tract viral load, and serum level of cytokines [16].

Convalescent serum was likewise utilized in the West African Ebola epidemic, 2013. A small nonrandomized study in Sierra Leone revealed fundamentally longer survival for those treated with convalescent whole blood comparative to those who received standard treatment[17]. Two patients transferred to the United States and treated with a combination of convalescent serum and an experimental drug also survived. WHO recently issued a timely ''InterimGuidance for National Health Authorities and Blood Transfusion Services''in September of 2014,[18] which provided a thorough guidance on donor selection, screening, donation, and handling of blood and plasma units for the use of convalescent whole blood or plasma from patients who recovered from EVD.It also included guidance on the transfusion of convalescent whole blood or plasma to EVD patients, including informed consent collection and patient monitoring. A by-product of this program was the scientific feasibility of producing protective monoclonal antibodies from EVD survivors using peripheral blood mononucleatedcells (PBMCs) from their donated blood. Rapid progress in recent years in isolating singleantigen-specific B cells from human PBMCs from which highly potent mAbsproducedought to allow for a similar process for the production of Ebola-specific mAb[19].

USE OF CONVALESCENT SERA IN RECENT OUTBREAK OF COVID-19 :

It can be usedfor either prophylaxis of infection or treatment of ailment. In a prophylactic mode, the advantage of improving convalescent serum administration is that it can forestall infection and resulting disease in those who are at high risk for disease, such as vulnerable individuals with underlying medical conditions, health care providers, and those with exposure to affirmed instancesof COVID-19.

Passive antibody administrationto prevent disease is as of now usedin clinical practice. For example, patients exposed to hepatitis B and rabies viruses are treated with hepatitis B immune globulin (HBIG) and human rabies immune globulin (HRIG), respectively. In addition, passive antibody is used for the prevention of severe respiratory syncytial virus (RSV) disease in high-risk infants. Until recently, a polyclonal hyperimmune globulin (RSV-IG) prepared from samples of donors with high serum titers of RSV neutralizing antibody was used, yet these preparations have now been supplanted by palivizumab, a humanized murine mAb. Used therapeutically, convalescent serum would be administered to those with clinical disease in an effort to their symptoms and mortality. The viability of these approaches cannot be inferred without carrying out a controlled clinical trial.

Based on the historical experience with antibody administration, it tends to be forseenthat antibody administration would be more effective in preventing disease than in the treatment of established disease[20].Since the proposeduse of convalescent sera in the COVID-19 epidemic would rely on preparations with high titers of neutralizing antibody against the same virus, SARS2-CoV-2, ADE might be far- fetched . The accessible evidence from the use of convalescent sera in patients with SARS1 and MERS [21], and episodicproof from its use in 245 patients with COVID-19 [22], recommend it is safe.

RISKS ASSOCIATED WITH THE USE OF CONVALESCENT SERA:

Risks of passive administration of convalescent sera ordered into two forms, known and theoretical. Known risks are those associated with transfer of blood substances, which incoporporate in advertent infection with another infectious diseaseagent and responses to serum constituents, including immunological reactions such as serum sickness. With modern blood banking techniques that screen for blood-borne pathogens and match the blood type of donors and recipients, the risks of inadvertently transferring known infectious agents or triggering transfusion reactions are low. However, convalescentsera used in a therapeutic mode wouldlikely be administered to individuals with pulmonary disease, in whom plasma infusioncarries some risk for transfusion related acute lung injury (TRALI) [23], and this ought to be a thought in the risk-benefit assessment.

The theoretical risk involves the phenomenon of antibody dependent enhancement of infection (ADE). In several viral diseases, ADE can occur and encompasses an upgrade of disease in the presence of certain antibodies. For coronaviruses, several mechanisms for ADE have been described, and there is the theoretical concern that antibodies to one type of coronavirus could enhance infection to another viral strain.[24]

Another theoretical risk is that antibody administration to those exposed to SARS-CoV-2 may prevent disease in a manner that attenuates the immune response, leaving such individuals vulnerable to subsequent reinfection. In this regard, passive antibody administration before vaccination with respiratory syncytial virus was accounted to attenuate. humoral but not cellular immunity[25].This concern could be explored major aspect of a clinical trial by measuring immune responses in those exposed and treated withconvalescent sera to prevent disease. If the risk proved real, these individuals could be vaccinated against COVID-19 when a vaccine becomes available.

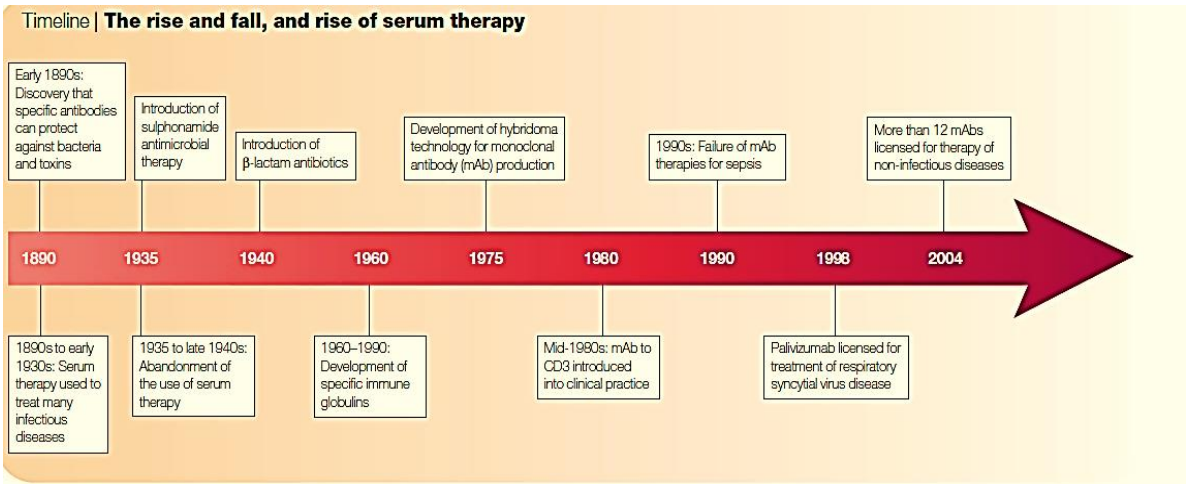

Figure 1: Use of serum therapy in infectious diseases [1].

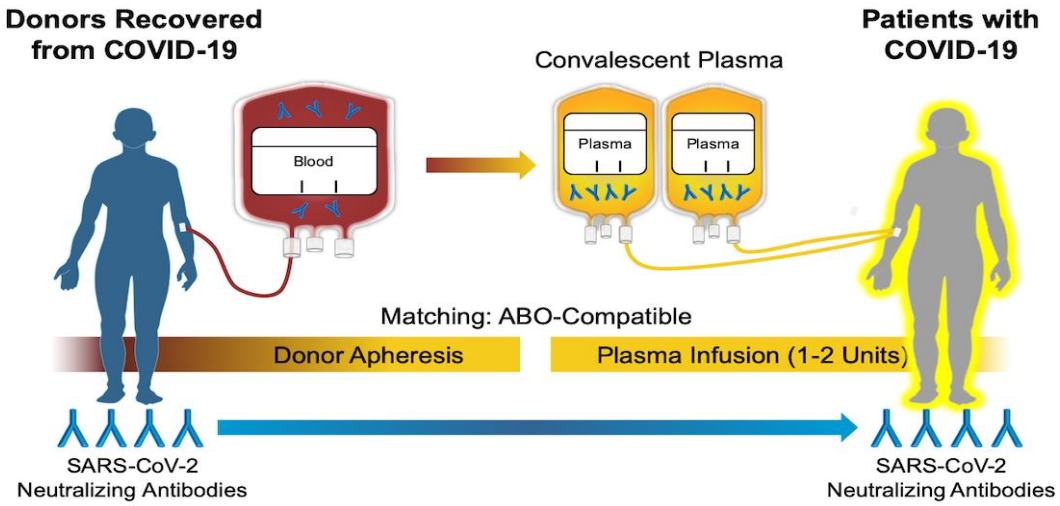

Figure 2.Schematic of the use of convalescent sera for COVID-19 [26].

RECOMMENDATIONS FOR INVESTIGATIONAL COVID-19 CONVALESCENT PLASMA:

On April 13, 2020 FDA has issued guidance to provide recommendations to health care providers and investigators on the administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency [27].The guidance provides recommendations on the following:

- Pathways for the use of investigational COVID-19 convalescent plasma
- Patient eligibility
- Collection of COVID-19 convalescent plasma, together with donor eligibility and donor qualifications
- Labelling, and
- Record keeping

As COVID-19 convalescent plasma has not yet been approved for use by FDA, it is regulated as an investigational product. FDA does not collect or provideCOVID-19 convalescent plasma. Health care providers or acute carefacilities would instead acquire COVID-19 convalescent plasma from an FDA-registered blood establishment.

DEPLOYMENT AND PROPOSED USE:

To deploy convalescent serum administration for COVID-19 the accompanying six conditions must be met[28].

(i) Availability of a population of donors who have recovered from the disease and can donate convalescent serum;
(ii) Blood banking facilities to process the serum donations;
(iii) Availability of assays, including serological assays, to detect SARS-CoV-2 in serum and virological assays to measure viral neutralization;
(iv) Virology laboratory support to perform these assays;
(v) Prophylaxis and therapeutic protocols, which should ideally include randomized clinical trials to assess the efficacy of any intervention and measure immune responses; and
(vi) Regulatory compliance, including institutional review board approval, which may vary depending on location. Ideally, the use of convalescent serum would involve multiple centers, follow randomized control protocols, and have a single center as a governing body. Each of these conditions should be available in developed areas affected by COVID-19.Recovery from COVID-19 willbe assessed clinically, and such individuals must be shown to free of SARS-CoV-2, including in their blood by appropriate viral nucleic acid screening. Donated blood products will be screened for infectious agents according to current blood banking practices, and individual sera will be studied for specific antibody content and neutralizing activity to SARS-CoV-2.Contigent upon the volumes needed and the neutralizing activity of donated convalescent sera, these could be pooled or used individually, and preparations for clinical use would be treated for pathogen attenuation.

CONCLUSION:

The use of convalescent plasma can provide immediate immunity against biological weapons has spurred the search for, and development of, protective antibodies against many selected agents including Middle East Respiratory Syndrome, Severe Acute Respiratory Syndrome (SARS), H1N1 flu, H5N1 flu, Ebola, Poleomyelitis, Measles. COVID-19 convalescent sera could be used to treat individuals with early symptoms and prevent disease in those exposed. FDA has issued guidance to provide recommendations to health care providers and investigators regarding administration and study of investigational convalescent plasma collected from individuals who have recovered from COVID-19 (COVID-19 convalescent plasma) during the public health emergency. Clearly, the use of convalescent serum would be a stopgap and alternate measure that could be used in the midst of the current pandemic.

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Conflicts of interest: The authors declare no conflicts of interest.

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