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Review Article

Immunotherapy As an Alternative for the Treatment of Covid-19 in Brazil: A Brief Review

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Abstract

Introduction: Since the beginning of the pandemic caused by SARS-Cov-2, much research has been done on possible treatments to combat the virus, but nothing has shown to be fully effective and the vaccination process in Brazil experienced financial and logistical difficulties in its course. In this context, Immunotherapy, already known and used clinically in the treatment of other illnesses, is one of the alternatives to be explored for the treatment of COVID-19, as it induces, through neutralizing antibodies, a rapid passive immunity in a short period of time. Among the available strategies are the use of Convalescent Plasma, Hyperimmune Equine Serum, Specific Intravenous Immunoglobulin G and Monoclonal Antibodies.

Methods: This review consulted the databases Scielo, Science Direct, PubMed and Google Scholar, from which 83 articles and 7 scientific texts, presented by public agencies, published from 2016 to 2021, were selected.

Results: The article identifies and discusses how immunotherapy works against the disease caused by SARS-Cov-2, what are the production technologies, benefits, risks, current limitations and their perspectives in the context of the Brazilian public health system.

Conclusion: Several pre-clinical and clinical studies in progress evaluate the safety and efficacy of these therapies in the clinical management of COVID-19. Of these, monoclonal antibody is the most promising and technologically advanced product available at the moment.

Keywords: blood products, human plasma, IVIgG, immunotherapy, mAb, SARS-CoV-2.

Introduction

In November 2002, the first case of atypical pneumonia that occurred in Foshan City (Guangdong Province, China) was reported. The disease spread rapidly to different countries, leading to the closure of commercial establishments, schools and the adoption of many restrictive measures to stem its progress. The World Health Organization (WHO) identified that the causative agent of severe respiratory syndrome was a new type of coronavirus, unlike any other member of the *Coronaviridae* family[1]

Nowadays, the pandemic caused by the new coronavirus is already one of the biggest health challenges faced by the

world in this century[2]. WHO recently declared South America as the new epicenter of the COVID-19 pandemic and Brazil has become one of the most affected countries, with a total of tens of millions of recorded cases so far[3]. While the vaccination process in the country still in progress, therapeutic strategies have been proposed as alternative treatment to patients affected by COVID-19, such as studies for the redirection of antiviral and anti-inflammatory drugs[4]. However, until now there is no drug capable of controlling the proliferation of the virus and the treatment of patients with COVID-19 is based on the control and relief of signs and symptoms[5].

In this context, Immunotherapy is one of the alternatives to be explored for the treatment of covid-19 by inducing, through neutralizing antibodies, a fast immunity, passively, in a short period of time[6,7].
In SARS-CoV-2 infection, neutralizing antibodies work by blocking the entry of the infectious agent into the host cell, as the antigen-antibody complex prevents the virus's "S" (or "spike") protein from binding to the angiotensin converting enzyme's (ACE-2) receptor and the fusion of viral and cell membranes occurs[8,9]. In addition, antibodies also play anti-inflammatory action and are able to activate other body defense factors such as pro-coagulant or antifibrinolytic factors[10,11]. Within this proposal, the main therapeutic strategies are the use of convalescent plasma, hyperimmune equine serum, intravenous immunoglobulin G and monoclonal antibodies. This review aims to identify how immunotherapy works against COVID-19, discuss production technologies, benefits, risks, current limitations and what are their perspectives in the context of the Brazilian public health system.

Methodology:

This is a literature review that used the databases Scielo, Science Direct, PubMed and Google Scholar, from which 83 articles and 7 scientific texts were selected and presented by public agencies, published from 2016 to 2021. In the research of the articles the descriptors COVID-19, SARS-CoV-2, immunotherapy, convalescent plasma, anti-SARS-CoV-2 intravenous immunoglobulin G, monoclonal anti-SARS-CoV-2 antibody, IgG purification were used.

Results and discussion:

Convalescent Plasma: Convalescent plasma can be defined as the liquid part of the antibody-rich blood of a cured or recovering patient of a disease of interest and can therefore be used as a therapeutic product after processing[12]. There are records of the use of convalescent plasma as a therapeutic alternative since the Spanish flu pandemic, between 1917 and 1919; in addition to other contagious respiratory diseases that do not have a specific treatment, following the recommendation of the World Health Organization[13].

To obtain convalescent plasma from individuals recovered from COVID-19, the donor's whole blood is collected in the blood center and the plasma component is separated, using the physical principle of centrifugation. After processing, the convalescent plasma is then transfused to the patient affected with the disease. The collection can also be done by plasma apheresis, a procedure in which a blood component is separated and removed from the organism through the use of automated equipment and immediately transfused to the receptor. With apheresis it is possible to obtain up to 800 mL of plasma from a single donation. This method helps to preserve the natural activity of the plasma and allows for a selective collection of the blood fraction[14,15,16].

Hyperimmune Equine Serum: Hyperimmune serum is an IgG-type immunoglobulin concentrate derived from the blood plasma of horses and used

therapeutically to neutralize viral antigens[17].

Serotherapy has historically been used to treat diseases such as tetanus, venomous animal accidents, and prophylactically in cases involving rabies virus-carrying animals[18,19]. Since the early years of this century, there have been studies that relate the use of hyperimmune serum to the treatment of viruses caused by the *Coronaviridae* family[20].

The production process takes place initially by inoculating the antigen in the horse. After the time necessary for the development of immunity, the animal's blood is collected, coagulated and centrifuged, in order to obtain plasma serum. This serum should undergo a treatment with fractionation steps, which involve protein precipitation by ammonia salts (salting out phenomenon) and digestion, in which pepsin is added to remove the Fc fraction of antibodies; as well as steps to reduce and inactivate the viral load, which may be by incubation at acidic pH and a final stage of sterilizing filtration, resulting in a biological product for intramuscular application[21,22,23].

Specific Intravenous Immunoglobulin G (IVIgG): Intravenous Immunoglobulin G (IVIgG) is a finished pharmaceutical product consisting of a G immunoglobulin concentrate isolated and purified from the plasma of healthy donors with high titer of specific antibodies against a particular pathogen[8].

IVIgG is used in the treatment of autoimmune diseases, primary and secondary immunodeficiencies, inflammatory and neuroimmune disorders, as well as in cases of sequelae related to infections[8].

In order to produce intravenous immunoglobulin G, the hemoderivatives industry collects plasma bags from blood centers and, from a pool, initiates the process of plasma fractionation by cold ethanol, cryoprecipitation or precipitation by polyethylene glycol (PEG). For the reduction and inactivation of the viral load, the fractionated plasma pool goes through the incubation steps in acidic pH, solvent/detergent treatment (0.3% tri-n-butyl phosphate and 1% polysorbate 80 to 37 °C) and pasteurization. Ion exchange chromatography or ultrafiltration can be used to purify the product. Finally, sterilizing filtration is performed[24,25].

Monoclonal Antibody (mAb): Monoclonal antibodies are selective antibodies to a specific viral antigen and are named because they are produced from a single clone of B lymphocytes[26]. They are biological products with high specificity and can have effector functions modulating different effects in the organism, depending on the pathogen[27]. The development of technologies capable of isolating and cloning antibodies has made it possible to expand its therapeutic use in the fields of oncology and autoimmune diseases[28]. Its production is made from mammalian cells, traditionally Chinese Hamster Ovary cells (CHO), prepared in the laboratory to express antibodies. These cells are grown in bioreactors for one or two weeks until the desired amount of antibodies produced by CHO cells is reached. Subsequently, the purification process of these antibodies, which can use centrifugation, filtration, affinity chromatography, or ion exchange, is initiated; followed by viral inactivation steps[29,30]. Monoclonal antibodies directed to different pathogens can be combined to achieve synergistic or additive effects and thus expand the possibilities of use[31,32]. Currently many preclinical and clinical studies are underway to evaluate treatments with monoclonal antibodies against hard-to-treat diseases such as AIDS, Ebola and COVID-19[33].

Immunotherapy and Vaccine: Immunotherapy consists in the administration of antibodies against a given

antigen, conferring a passive immunity. On the other hand, vaccination provides an active immunization, which takes time, depending on each organism, to fully develop[34]. For this reason, immunotherapy can be considered as a means of providing immediate immunity to people susceptible to a particular disease. A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for disease treatment. When used for therapy, the antibody is most effective when administered shortly after the onset of symptoms[35].

Convalescent Plasma as the First Immunotherapeutic Strategy Against Covid-19: Historically, convalescent plasma is used as a therapeutic or prophylactic strategy in cases where there is no specific treatment for a disease, as it may be available once a minimum number of recovered patients who are fit to be plasma donors containing antibodies is reached[36]. Its use dates back to 1890, when a pool containing polyclonal antibodies was first used to protect against bacterial toxins before the introduction of antimicrobials[37]. This therapy was successful during epidemics of the H1N1[38] and Ebola[39] viruses, in which the group of patients in whom convalescent plasma was administered achieved a reduction in mortality levels; and MERS-CoV, the causative agent of the Middle East Respiratory Syndrome, in which researchers began to track specific antibodies in convalescent plasma, using ELISA immunoenzymatic test, in an attempt to prove the effectiveness of this immunotherapy[40].

Regarding the use of Convalescent Plasma in the treatment of COVID-19, studies evaluated an improvement in the clinical status of patients affected by SARS-Cov-2 virus[41,42,43], however, the small number of the analyzed sample and the lack of a control group make necessary new randomized clinical trials, well delineated, with a more significant "n" of participants; to be sure of the validity and effectiveness of the method[44]. A study by Ferrari *et al.* also suggests that patients with COVID-19 who had hematological disorders and were immune depressed due to chemotherapy, showed a good tolerance to treatment with convalescent plasma and that this therapy contributed to their clinical improvement[45]. The protocol used in clinical studies consists of the administration of one or two units of convalescent plasma, depending on the body mass index, with volume of about 200 mL, during 1 hour of transfusion[46]. It is recommended that the timeliest administration period is in the first 7 days; there is a good efficacy within 14 days and is no longer indicated beyond three weeks after the onset of the disease. It is important that therapy is performed during the viral replication stage[47].

Although its efficacy and safety have not yet been fully proven, treatment with Convalescent Plasma may be a valid option in the treatment and / or prophylaxis of various infectious diseases, both in association with other preventive measures, and as the only therapy when a specific treatment is not available[48,49]. This explains the fact that it was one of the first treatments used against COVID-19. It does not usually cause significant adverse effects, but some patients reported shivering and low fever after transfusion[50]. In rare cases, there may be phlebitis, generalized jaundice and anaphylaxis[51]. Focosi suggests that a convalescent plasma unit may contain different soluble factors from which benefits can be expected, such as anti-inflammatory cytokines or, in ABO-compatible units, anti-A isoagglutinins, which apparently inhibit the entry of SARS-Cov-2 in the human cell[52]. Its main limitation is the low number of donors with high antibody titers available[53]. As a disadvantage, it is possible to cite short-term protection, according to the time that

antibodies remain circulating in the bloodstream[54] and the lack of standardization, since it is not based on a standardized product, given that plasma samples are not grouped and used individually[33]. Finally, there are non-infectious risks associated with transfusion, including transfusion reactions such as acute pulmonary injury associated with transfusion, which can worsen respiratory disease in COVID-19, especially those who are already using supplemental oxygen and/or intubated[55].

The Production of Hyperimmune Equine Serum Anti Sars-Cov-2 in Brazil: Hyperimmune equine serum, which consists of a concentrate of heterologous polyclonal antibodies, formed by intact immunoglobulin G (IgG) molecules or with the digested Fab portion, with F(ab')2 fractions[56]; has been commonly used for post prophylaxis -exposure as in the cases of tetanus, diphtheria, or rabies; and in emergencies caused by infectious diseases that can be prevented and treated by antimicrobials[57].

The first study using the hyperimmune serum of horses dates from the end of the 19th century, in which the researcher Émile Roux managed to successfully treat cases of tetanus, pneumonic and bubonic pests, but it was the Brazilian physician Vital Brazil who first demonstrated the relationship between antigenic specificity and treatment with serotherapy. Since then, this has become the established therapy against animal venom, or prophylactically in patients carrying rabies virus; where plasma or serum equine is used as a source of polyclonal antibodies[58]. In Brazil, the Vital Brazil Institute, the Butantan Institute and the Ezequiel Dias Foundation are the main centers producing hyperimmune serum[21]. Currently, a hyperimmune serum produced from the immunization of horses exposed to viral trimetric S proteins is being produced at the Vital Brazil institute, in partnership with the Federal University of Rio de Janeiro (UFRJ)[59,60].

The anti SARS-Cov-2 serum developed by Brazilian researchers so far has been shown to be effective in in vitro assays. The F(ab') 2 concentrate was able to recognize the trimeric S protein, both in the ELISA test, displaying a titer of 1:1,000,000, and in cell culture, binding specifically to infected cells. Neutralizing titers also reached high values: 1:32,000, about 100 times more than the neutralizing titers of the convalescent plasmas of three patients recovered from COVID-19, used for comparison purposes[60]. In May 2021, the Brazilian Health Surveillance Agency authorized the beginning of clinical research in humans with the anti-SARS-CoV hyperimmune serum developed by the Butantan Institute. Thus, it will be possible to produce reliable data on the safety and efficacy of the product[61] (ANVISA, 2021).

The production of heterologous polyclonal antibodies, such as hyperimmune equine serum, has been undergoing modernization processes since it was first used, in 1890, in order to increase safety for those who use it; following the guidelines of the World Health Organization (WHO) for production, control and regulation[62] (WHO, 2017). This therapy presents risks of hypersensitivity reactions and, in rare cases, anaphylactic reactions. However, the animals used as bioreactors are increasingly controlled, monitored, kept in isolation and constantly evaluated. When they began to be produced, these serums generated products that contained fractions of other animal proteins that were not IgG, favoring the manifestations of adverse reactions. Over the years, technical-scientific advances have enabled productive technologies to incorporate immunoglobulin digestion processes and new purification techniques[63]. Each manufacturer uses its own production route, but the digestion of immunoglobulins provided to be a necessary step, as it

promotes the removal of the Fc fraction, along with other non-specific proteins; which increases the degree of purity and decreases possible inflammatory responses of the organism, mainly reactions of the type Antibody-Dependent Enhancement (ADE), which will be discussed later in this article (Section 3.10).

IVIgG Therapy for Covid-19 and Associated Diseases: Characterized as a hemoderivative drug obtained from a pool of human plasma containing homologous antibodies purified by physicochemical processes, intravenous Immunoglobulin G (IVIgG) provides passive immunological protection against a wide range of pathogens and is the first line therapy for many autoimmune and inflammatory diseases[64]. Because it has a standardized concentration of neutralizing IgG's per volume, measured by viral neutralization test, it is considered of a superior quality to convalescent plasma. It is recommended that IVIgG should replace convalescent plasma in therapy as soon as it becomes available[57].

Regarding SARS-Cov-2 infection, a case study conducted in China[65] evaluated the prognosis evolution of three patients affected by COVID-19, considered in severe condition by the medical team, using high doses of intravenous immunoglobulin G: 0,3-0,4 g/kg/day for 5 days. All of them had normalization of temperature within two days of treatment and relief of respiratory symptoms within five days. However, two of these patients had concomitant use of antiviral drugs and the third, steroids; which the authors consider to be a confounding factor.

In a multicenter cohort study[66], Shao *et al.* evaluated the efficacy of IVIgG in severe COVID-19 patients admitted to a Chinese hospital. Of the 325 patients, 174 received IVIgG along with additional therapies, which included antibiotics, antivirals and corticosteroids. Comparison with the control group showed that the use of high doses of IVIgG (0.1-0.5 g kg/day/during 5-15 days) resulted in an improvement of patients in critical condition[66]. Another retrospective study[67] by Xie *et al.* also confirmed the therapeutic benefits of IVIgG against SARS-Cov-2 when the therapy is initiated early: the reduction of the use of mechanical ventilation, reduction of hospital stay-time and improvement of the prognosis, with faster recovery of patients[67]. Phase 2, 3 and 4 double-blind randomized Clinical Trials are registered in the United States, France, Spain, China and Ukraine (NCT04500067, NCT04411667, NCT04480424, NCT04432324, NCT04350580, NCT04400058, NCT04261426, NCT04403269) [64]. This method of analysis may provide more reliable data regarding the effectiveness of this treatment. It is important to note that immunoglobulins collected in different countries or continents may vary among themselves, as lifestyle, diet and the environment play an important role in the development of specific antibodies against the virus. Thus, it would be ideal to treat infected patients using IgG's collected in the same demographic region, to increase the chances of viral neutralization[68].

SARS-Cov-2 infection can also trigger complications such as autoimmune and inflammatory diseases, including pediatric inflammatory multisystem syndrome, Guillain-Barre syndrome, and idiopathic thrombocytopenic purpura. IVIgG therapy, since it is traditionally used for this purpose, would benefit patients with these rare pathological manifestations associated[69,70].

Compared to heterologous antibody therapy, homologous antibodies have the advantage of provoking fewer adverse reactions. However, there may be a difficulty in finding suitable donors with sufficient antibody titers for the production of IVIgG[21].

Therapy with Monoclonal Vs. Polyclonal Antibodies: The current use of monoclonal antibodies (mAbs) for COVID-19 is limited

to bedside administration in controlled clinical trials. During pre-clinical trials, it was demonstrated that passive antibody transfer occurred in animal models[71]. Initial results in human patients were also promising. Two randomized, double-blind clinical trials aimed at assessing whether monoclonal antibodies are effective in preventing SARS-Cov-2 infection are currently being conducted in the United States. The first (NCT04497987) indicated a low incidence of severe cases in patients treated with LY-Cov555 (Bamlanivimab) compared to the group that used placebo[72] (LILLY, 2020). In the second (NCT04452318), the cocktail of REGN-COV2 antibodies (Casirivimab) quickly reduced viral load and symptoms associated with COVID-19 in hospitalized patients[73] (REGENERON, 2020). Currently these trials are in phase 3 and involve adults who are at risk of infection due to close contact with people with SARS-Cov-2 infection[74] (NIH, 2020). Likewise, monoclonal antibodies have shown promising results for use in the treatment of COVID-19, in addition to prophylactic use. In 2020 Russia approved, for emergency use, the use of Levilimab in patients hospitalized with COVID-19, which managed to significantly reduce the number of deaths from the disease[75] (BIOCAD, 2020). Kaplon estimates that there are more than 200 clinical trials in progress between phases 2 and 3 that use mAbs therapeutically or prophylactically[71].

The advantages and disadvantages of monoclonal antibody therapy compared to polyclonal antibodies are well discussed in the literature. mAbs can reduce the risk of contamination by pathogens that may not be detected in polyclonal antibody products[33]. In addition, mAbs can be redesigned in the laboratory in order to have their characteristics more refined, as is the case of antibodies made up of a single variable heavy chain (nanobodies); conjugated to other drugs; bispecific; or those that have their Fc fraction modified to prevent the triggering of ADE reactions[76,77,78]; and its production can be expanded and mass-produced by *in vitro* cultures.

In contrast, by targeting a specific epitope, monoclonal antibodies may lose their effectiveness in case of mutations of the SARS-Cov-2 virus, which is a major disadvantage[79]. Targeting the site of infection is another important obstacle. Because the immunoglobulin isotope used in the production of most commercially available human mAbs is IgG type 1, which has limited access to mucosal tissues, achieving relevant concentrations in sites such as the respiratory tract is a challenge to be overcome in the development stage of these drugs[26].

The financial issue must also be taken into account, since the production of mAbs is more expensive in relation to polyclonal antibodies, and may limit access to medication to a part of the population[80,81].

Table 1 presents a comparison between the different immunotherapeutic strategies for the treatment of COVID-19.

The Challenge of Ade Reactions in the Administration of Immunotherapy: The SARS-Cov-2 virus penetrates the host cell through its S protein (transmembrane peak glycoprotein), which forms a homotrimer, projects from the viral surface and binds to the angiotensin-2-converting enzyme receptor (ACE-2) expressed on the surface of epithelial cells, including those located in the airways. The host receptor binding process is mediated by the S1 subunit through the receptor binding domain (RBD). After binding to the ACE-2 receptor, the proteolytic activation of the S2 subunit is responsible for the fusion between the viral and cellular membranes[82].

Neutralizing antibodies act by binding to the S1 and S2 subunits of the SARS-CoV-2 virus, preventing its coupling to the ACE-2 receptor and subsequent viral penetration

and replication in the host cell[8]. Immunoglobulins may also target the cytokine storm that occurs in COVID-19, by reciprocal regulation of effector cells Th1, Th17; regulatory T cells; and inhibition of the activation of innate immune cells and secretion of inflammatory mediators, with the reduction of IL-6 and C-reactive protein[64]. However, the quality and quantity of the antibody response influence the functional results. High affinity neutralizing antibodies can block the pathogen's action, but large proportions of non-neutralizing antibodies and early serum conversion are reported to be correlated with increased disease severity in patients with COVID-19 through an antibody-dependent exacerbated reaction, or ADE reaction[83]. Firstly proposed as an underlying effect of hemorrhagic dengue fever[84], the mechanism of ADE reactions is not completely understood, but it is known that in these cases low quality, low quantity and non-neutralizing antibodies bind to virus particles through the Fab domain. , while the coupling of the Fc domain and Fc domain receptors (FcRs) expressed in lung monocytes and macrophages facilitates viral penetration into the host cell and signals the activation of a storm of pro-inflammatory cytokines such as L-1β, IL- 2, IL-6, IL-17, IL-8, TNF and CCL-2; triggering systemic hyperinflammation and exerting the opposite effect to neutralizing immunoglobulins[71,85]. This structure determines the development of a Systemic Inflammatory Response Syndrome (SIRS) with increased damage to pulmonary ventilatory capacity that results in severe fibrosis[86,87,88]. It is believed that there is a genetic predisposition for this type of response, and further studies are needed to clarify the reasons why some patients with SARS-CoV-2 develop SIRS[47,89].

Theoretically, ADE-type reactions may exacerbate COVID-19 infection in patients who have used immunotherapeutic drugs that have not been tested for SARS-CoV-2-specific neutralizing antibodies. In addition, administration of passive antibodies can suppress the humoral immune system of the receptor from generating pathogen-specific antibodies, leaving the individual susceptible to reinfection, as in a negative feedback[90]. To prevent the occurrence of ADE-type reactions, the production of immunotherapeutic drugs already includes the removal of the Fc fraction of specific immunoglobulins against the SARS-CoV-2 virus[21].

Conclusions: In order to combat the increasing number of COVID-19 cases in Brazil, as well as the high rate of deaths caused by the disease, the advent of vaccines is undoubtedly the best long-term immunological approach. However, in the current epidemiological and health emergency, it is necessary to propose more emergency solutions, such as Immunotherapy. In addition, future generations may benefit, in possible health crises, from the development of immunotherapeutic drug production technologies, which have the potential to aid in the prophylaxis and treatment of various viral diseases, infectious, autoimmune and inflammatory. Among the different immunotherapeutic strategies currently under study for the treatment of COVID-19 are convalescent plasma, hyperimmune serum, specific immunoglobulin G, and monoclonal antibodies. Of these, monoclonal antibody is the most promising and technologically advanced product available at the moment. Immunotherapeutics are life-saving biological drugs. Now the results of clinical trials conducted at the moment will be fundamental to prove their efficacy and safety in the clinical management of COVID-19.

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