Cell-Free Immunotherapies-Effective Approaches Against COVID-19

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Abstract: In 2019, an infectious coronavirus disease, known as COVID-19, was discovered to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The highly contagious nature of the virus led the scientific community to urgently develop therapeutic approaches for fighting against SARS-CoV-2. The mechanisms of COVID-19 are lung damage and dysregulated immune response. This article attempted to systematically review the available literature on cell-free immunotherapeutic strategies against COVID-19, shedding light on our understanding of COVID-19. Cell-free immunotherapy methods still have room for improvement, and understanding the immunology of COVID-19 is crucial for developing therapeutic strategies. As a result, cell-free immunotherapy could be used more appropriately, which may help scientists to determine the direction of future research.

1 INTRODUCTION

In 2019, the contagious disease COVID-19 rapidly became a global pandemic and has to this date caused approximately 260 million infections and 5 million deaths around the world. SARS-CoV-2 is recognized as a novel beta coronavirus (β CoV), which is a single-stranded RNA virus. The mechanisms of COVID-19 are cytopathological damage of the cell and dysregulated immune response. Despite the fact that many people infected with the coronavirus might experience organ dysfunction (Figure 1), they could recover without hospitalization. By contrast, the elderly and immunocompromised are more likely to develop serious illnesses or face a higher risk of mortality. Therefore, the highly contagious nature of SARS-CoV-2 led the scientific community to urgently develop therapeutic treatments for combating SARS-CoV-2. Immunotherapies are effective methods for combating viral infections by inducing, enhancing, or suppressing the immune response. Immunotherapies include cell-based therapies and cell-free therapies. Cell-based therapies aim to inject a donor's healthy cells into a patient's body to fight against disease. Cell-free therapies have advantages in overcoming the risks associated with cell-based therapies, such as macro thrombosis and micro thrombosis. Therefore, Cell-free therapies are safer, cheaper, and more beneficial to humans. Current cell-free immunotherapies include corticosteroids, interferons, monoclonal & polyclonal antibodies, and other cell-free immunotherapies (Figure 2). This article reviewed these cell-free immunotherapy techniques against SARS-CoV-2 and discussed current peer-reviewed cell-free immunotherapeutic strategies against COVID-19.
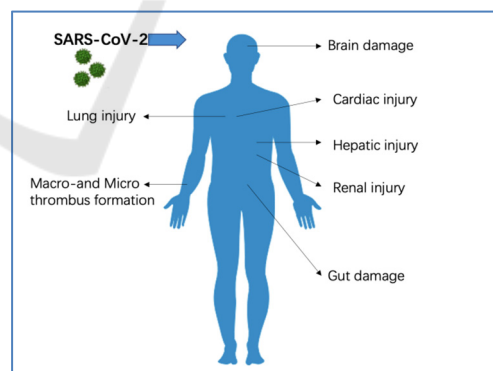

Figure 1: Organ damages caused by the SARS-CoV-2 can be solved by cell-free immunotherapies: cell-free immunotherapies might mitigate cardiac, kidney, liver, nervous system, and lung injury; decrease macro- and micro-thrombus formation and endothelial inflammation; and repair lung epithelial and endothelial cells.
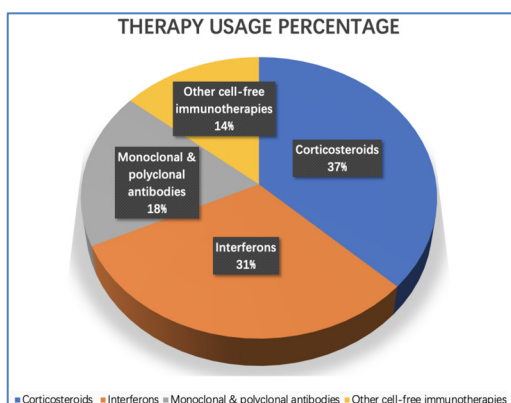
Figure 2: Graphical representation of usage percentage of cell-free immunotherapies for COVID-19, which data were from surveys in Chinese hospitals.

2 CORTICOSTEROIDS FOR COVID-19

Patients infected with coronavirus disease have a severe immune response leading to acute lung injury and acute respiratory distress syndrome (ARDS) (Erika, 2021). Among the cell-free drugs that target the immune system, corticosteroids are usually used to mitigate inflammation by suppressing the immune system in severe cases of coronavirus disease including SARS, MERS and COVID-19. Corticosteroids are artificial drugs that are known as steroids, which are naturally produced in the adrenal cortex of vertebrates. They could be used in the management and treatment of almost all areas of medicine.

On the one hand, WHO claimed that systemic corticosteroids are powerful immunomodulators, which are generally low-cost, easy to administer and accessible in healthcare systems pressured by the COVID-19 global pandemic (WHO, 2020). Some studies reported signs of beneficial effects of corticosteroids through evidence comparing systemic corticosteroid use to usual care in COVID-19. The recovery trial demonstrated a lower 28-day mortality in patients who received corticosteroids and were either receiving oxygen alone or receiving invasive mechanical ventilation, compared to usual care (WHO, 2020). It was shown that the superior potency of corticosteroids against COVID-19, because they could lower the fatality rate and reduce the need for receiving invasive mechanical ventilation.

On the other hand, systemic use of corticosteroids has potential harms, such as hyperglycaemia (especially in diabetics), hypernatremia,

gastrointestinal bleeding, neuropsychiatric effects, neuromuscular weakness, superinfection, immunocompromise, stroke or myocardial infarction (WHO, 2020). Additionally, there is reason to suspect that systemic corticosteroids may also delay viral clearance and increase possibilities of secondary infections, even though there is no firm data and conclusion that could be drawn from studies and research. As a result, this method is not recommended for all patients, especially those who have mild/non-severe/moderate symptoms associated with COVID-19, because the adverse effects of mass use of corticosteroids may have more disadvantages than advantages.

On September 2, 2020, the WHO made a strong recommendation for systemic corticosteroids in severe and critical COVID-19 based on the moderate certainty of evidence which showed a reduction in mortality of 3.4% in patients with COVID-19 who were critically or severely ill (WHO, 2020). In addition, WHO made a conditional recommendation not to use corticosteroids in the treatment of patients with non-severe COVID-19. The reasons were low certainty evidence which suggested an increased 28-day mortality in patients with non-severe COVID-19; that systemic corticosteroid use has potential harms (e.g. hyperglycaemia, neuromuscular weakness, superinfection); that indiscriminate use of the therapy for COVID-19 may potentially rapidly deplete global resources, and deprive patients who may benefit from it most (WHO, 2020). Ultimately, the impact of systemic corticosteroids in COVID-19 still remains unknown and controversial, which means that further investigations and trials on exploring the roles of the corticosteroid therapy in the management of patients are necessary. The clinical use of corticosteroids should be more conscious about inconclusive adverse events from corticosteroid administration in severe COVID-19 cases.

3 INTERFERONS

Interferons (IFNs) are proteins generated by a plethora of cells through the inflammatory response to viral infections. In a typical scenario, virus-infected cells release interferons, which kick off fundamental cellular defense mechanisms in nearby cells, such as heightening their antiviral defenses. There are three types of IFNs: alpha, beta and gamma. IFN-alpha is from leukocytes infected with the virus, IFN-beta is produced in fibroblasts infected with the virus, and IFN-gamma is induced by the stimulation of lymphocytes.

Type I IFNs have potentially positive effects for fighting against coronaviruses. Type I IFNs are famous for their antiviral and immunomodulatory properties, and they are usually used for limiting the spread of infectious agents, enhancing antigen presentation, and triggering the adaptive immune response. Studies showed the effectiveness of IFNβ against viral infections compared to IFNα. For example, a recent study published by Scientific Reports assigned patients randomly in a 1:1:1 ratio to IFNβ1a, IFNβ1b, or the control group (Ilad, 2021). Through comparing IFNβ1a and IFNβ1b against each other and a control group, IFNβ1a was associated with a significant difference against the control group while the IFNβ1b indicated no significant difference compared with the control group (Ilad, 2021). In general, mortality was indeed lower in both of the intervention groups: 20% lower mortality in the IFNβ1a group, 30% lower mortality in the IFNβ1b group and 45% lower mortality in the control group (Ilad, 2021). Also, these three groups did not show significant differences regarding adverse effects (Ilad, 2021). Given the limits of this study, further confirmation in larger studies was required. In addition, Sheahan et al found potent inhibition of MERS-CoV with IFNb (Timothy, 2020). Some other researchers conducted a preliminary study on 22 SARS patients. Comparing patients treated with corticosteroids alone, this study indicated the potential effect of interferon alfacon-1 combined with corticosteroids (Mona, 2004). Therefore, the studies on different types of viruses inferred that interferon could be able to be protective in treating patients with SARS-CoV-2.

However, such research on interferon therapy in SARS-CoV is far from enough, especially given that the virus is highly mutable and keeps changing. Interferon might not contribute beneficial results for hospitalized patients with COVID-19 (National Institutes of Health, 2021). Nevertheless, these findings still had clinical importance. For example, the combination of interferon and other therapies may be helpful for patients fighting COVID-19.

4 MONOCLONAL & POLYCLONAL ANTIBODIES

Through different ways in which antibodies are created from lymphocytes when an infection occurs, antibodies are classified into two main types: monoclonal and polyclonal. Both play important roles in the humans' immune system, diagnostic exams, and treatments. Polyclonal antibodies (pAbs) are a heterogeneous mixture induced by different B cell lineages within the human body, whereas monoclonal antibodies (mAbs) are secreted by identical B cells which are clones from a single parent cell. In addition, unlike polyclonal antibodies which are from live animals, monoclonal antibodies are produced in vitro environments using tissue-culture techniques. The main source of protective pAbs is recovered patients, whose plasma could be given to patients infected with COVID-19 as a treatment practice. In contrast, experimental methods usually produce antiviral murine, humanized mAbs, or their fragments. In general, when exposed to a pathogen, the majority of antibodies produced by the humoral immune system can target certain antigenic determinants with sufficient affinity if they are protective, and some antibodies target domains in the spike protein can yield protection. This is how antibodies prevent the reproduction of the virus or its variants. Emergency use of antibody drugs should be allowed in order to help patients' immune systems fight against viruses.

Scientists expected that pAbs and mAbs could be useful in reducing viral levels, minimizing damage to the patients' lungs, preventing COVID-19 early-stage infections, and allowing non-hospitalized patients to heal more rapidly (Michael, 2021). This treatment has long worked better on individuals who have higher virus levels. However, the role of this treatment is still controversial. Scientists are still researching the population of patients who can benefit the most from this treatment, and the extent that this treatment is effective.

5 OTHER CELL-FREE IMMUNOTHERAPIES FOR COVID-19

Although there still remain ambiguities in the three main COVID-19 therapies above, several other approaches have meaningful results. The following section discussed other possible treatments for patients with COVID-19.

5.1 Convalescent Plasma Therapy

Convalescent plasma therapy transfers pathogen-specific antibodies from recovered patients to help others recover from the same illness. In response to SARS-CoV-2 infection, convalescent plasma therapy was useful when helping hospitalized patients to

recover and helping non-hospitalized patients to prevent disease. Convalescent plasma therapy is accessible because requirements for this therapy's infrastructure and resources are low. This therapy only requires the donated plasma from disease survivors and the standard blood collection infrastructure. Thus, convalescent plasma therapy could be readily used in low-resource settings around the world. In addition, convalescent plasma therapy could be given to hospitalized patients who have a weakened immune system and are infected with SARS-CoV-2. Convalescent plasma therapy could help them to recover from COVID-19 by lessening the severity and shortening the time of infection.

Recent studies, which have limited numbers of patients and do not have control groups, tested the clinical efficacy of convalescent plasma therapy in fighting against COVID-19. To be more specific, the study reported the results of the treatment of five critically ill patients with COVID-19 with convalescent plasma in China (Shen, 2020). After receiving convalescent plasma therapy, four patients' clinical status improved within 12 days, with improvements such as enhanced PaO2/FiO2 and decreased viral loads (Shen, 2020). This study indicated that using convalescent plasma therapy has potential to fight against COVID-19, but it must be noted that this study did not have a control group. Moreover, it is important to note that the passive immunotherapy with convalescent plasma therapy has the most effective therapeutic effects when the viral load is relatively lower. Furthermore, this study initiated convalescent plasma therapy from ten to twenty-two days after admission of patients. Studies received favorable results showing that convalescent plasma therapy initiated earlier might have higher efficacies (Shen, 2020). Furthermore, compared with therapeutic uses, passive immunotherapies with convalescent plasma therapy have a better efficiency when used prophylactically. It is indicated that scientists should put more effort into investigating convalescent plasma therapy, especially as vaccines have already become available around the world.

There are still uncertainties regarding the roles of convalescent plasma therapy because the study by Shen et al. was a randomized controlled trial. Meanwhile, the results were based on limited evidence so far. Thus, the clinical and therapeutic impacts of plasma efficacy still need to be confirmed in the future studies and well-designed clinical trials.

5.2 Intravenous Immunoglobulin (IVIg)

IVIg is the use of a mixture of antibodies from donors that can be given intravenously. These antibodies are protective proteins produced by the human immune system in response to the presence of several pathogens, such as viruses, bacteria, parasites, and tumor cells. Donors' antibodies bind directly with the abnormal host pathogens, stimulating their removal.

Previous studies on SARS indicated that IVIg has benefits on SARS patients. A study performed by Wang et al showed that IVIg therapy improved leukocyte/platelet counts in patients with severe leukopenia, thrombocytopenia, and elevated levels of aminotransferase, lactate dehydrogenase, and creatine kinase (Wang, 2004). In addition, IgM-enriched IVIg therapy demonstrated benefits in patients with COVID-19 who were not cured by corticosteroid therapy. And a multicenter retrospective cohort study revealed clinical efficacy of intravenous immunoglobulin therapy in critical patients with COVID-19 from analyses on more than three hundred patients (Shao, 2020). This study showed that high dose IVIg could be helpful in the prognosis if administered in the early stage of the disease (Shao, 2020). A research meta-analysis retrieved four clinical trials and three cohort studies including 825 hospitalized patients (Xiang, 2021). In the critical subgroup, IVIg could reduce the mortality compared with the control group. However, the severity of COVID-19 was not related to the efficacy of IVIg. There was no significant difference in the severe or non-severe subgroups. In a word, IVIg may be clinically efficient in patients with COVID-19, but impacts and roles of IVIg therapy in COVID-19 treatments are still uncertain, and further effectiveness of it needs to be explored.

Adverse effects associated with IVIg are commonly muscle pain, blood clots, kidney problems, anaphylactic reactions and hemolytic anaemia. However, the role of IVIg in infected patients remains inconclusive because it is difficult to isolate its benefits as it has been used in combination with other drugs. In detail, patients with COVID-19 were benefited by mild dose corticosteroid plus IVIg therapy (20 g/day), even though they did not benefit from low dose IVIg therapy (10 g/day) (George, 2020). In addition, researchers found that the combination of IVIg and methylprednisolone could reduce respiratory morbidity in COVID-19. Further studies about therapeutic impacts of IVIg still need to be conducted, because the specific functions and effectiveness of IVIg still need to be confirmed through future research.

6 CONCLUSIONS AND OUTLOOK

On January 30, 2020, the World Health Organization declared the COVID-19 outbreak as a Public Health Emergency of International Concern, and later, as a pandemic on 11 March 2020. From when SARS-CoV-2 first emerged, it has spread so swiftly that the need to find effective COVID-19 therapies became necessary and urgent. In the evaluation of current COVID-19 therapies, patients' safety should be the main consideration. This paper summarized the most recent research and studies of cell-free immunotherapy, showing that this therapeutic intervention is proven to be useful against SARS-CoV-2. Despite this therapy's initial success, research on it still showed ambiguities and room for improvement. An overview of the advantages and disadvantages of these novel potential therapies that need to be formally tested in future clinical trials are presented in Table1, and the applicable conditions are summarized in Figure 3, indicating that among these methods, monoclonal & polyclonal antibodies are the most widely applicable, corticosteroids have biggest most potential, and there are still room for breakthroughs in interferons in the future.

Moreover, it is vital to note that the virus is changing. The Delta and Omicron variants appeared successively in 2021. The Deltacron variants appeared in 2022. Researchers must adapt their therapies with the new mutations in mind. Though there still remain challenges and uncertainty, this article attempts to provide a systematic overview of the available literature on cell-free immunotherapeutic strategies, with the aim to help scientists who investigate effective controls and novel treatments for COVID-19. It is significant to understand the intricacies of the virus-immune system in order to treat and manage disease properly in the future.

Table 1: Current cell-free immunotherapies for COVID-19 introductions and their potential beneficial & adverse effects in COVID-19.

Type	Introduction	Advantages	Disadvantages
Corticosteroids	Corticosteroids are artificial drugs that are known as steroids, which are naturally produced in the adrenal cortex of vertebrates.	Low cost; easy to administer and accessible in healthcare systems.	Potential harms, such as hyperglycaemia (especially in diabetics), hypernatremia, gastrointestinal bleeding, neuropsychiatric effects, neuromuscular weakness, superinfection/immunocompromise, stroke or myocardial infarction.
Interferons	There are three types of interferons (IFN): alpha, beta and gamma. IFN-alpha is from leukocytes infected with the virus; IFN-beta is produced in fibroblasts infected with the virus; IFN-gamma is induced by the stimulation of lymphocytes.	Limiting the spread of infectious agents, enhancing antigen presentation, and triggering the adaptive immune response.	Research on interferon therapy in SARS-CoV is far from enough, especially given that the virus is highly mutable and keeps changing. Interferon might not contribute beneficial results for hospitalized patients with COVID-19.
Monoclonal & Polyclonal Antibodies	Polyclonal antibodies (pAbs) are a heterogeneous mixture induced by different B cell lineages within the human body, whereas monoclonal antibodies (mAbs) are secreted by identical B cells which are clones from a single parent cell.	Useful in reducing viral levels, minimizing damage to the patients' lungs, preventing COVID-19 early-stage infections, and allowing non-hospitalized patients to heal more rapidly.	The role of this treatment is still controversial.

| Convalescent Plasma therapy	Convalescent plasma therapy transfers pathogen-specific antibodies from recovered patients to help others recover from the same illness.	Lessening the severity and shortening the time of infection.	There are still uncertainties regarding the roles of convalescent plasma therapy.
IVIg (Intravenous Immunoglobulin)	IVIg is the use of a mixture of antibodies that can be given intravenously. IVIg gives antibodies that the human body is not making on its own but can fight infections.	IVIg may be clinically efficient in patients with COVID-19.	Clinical and laboratory data on severe acute respiratory syndrome (SARS) are limited. Adverse effects associated with IVIg are commonly muscle pain, blood clots, kidney problems, anaphylactic reactions and hemolytic anaemia.
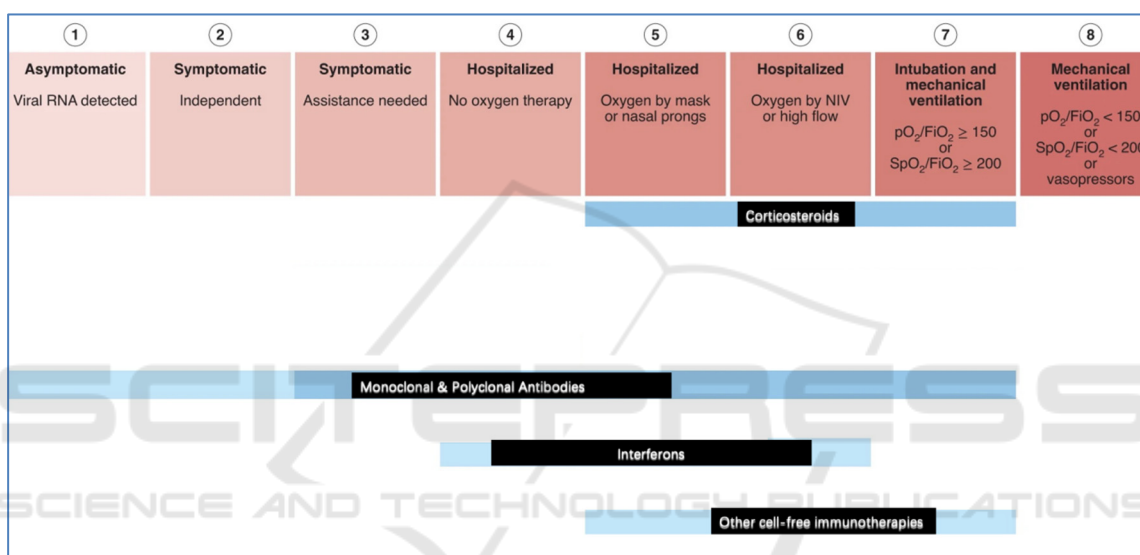
Figure 3: An overview of the options for cell-free immunotherapies in patients with COVID-19 depending on the stage of the disease, according to WHO Clinical Progression Score (Frank, 2022). The treatments based on high-quality randomized trials are presented in dark blue, while the more speculative treatments based on observational or small case-series studies are presented in light blue.

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