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COVID-19 immunotherapy: Treatment based on the immune cell-mediated approaches

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ABSTRACT

Multiple efforts are currently underway to control and treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19) worldwide. Despite all efforts, the virus that emerged in Wuhan city has rapidly spread globally and led to a public health emergency of international concern (PHEIC) due to the lack of approved antiviral therapy. Nevertheless, SARS-CoV-2 has had a significant influence on the evolution of cellular therapeutic approaches. Adoptive immune cell therapy is innovative and offers either promising prophylactic or therapy for patients with moderate-to-severe COVID-19. This approach is aimed at developing safety and providing secure and effective therapy in combination with standard therapy for all COVID-19 infected individuals. Based on the effective results of previous studies on both inflammatory and autoimmune diseases, various immune cell therapies against COVID-19 have been reviewed and discussed. It must be considered that the application of cell therapy for treatment and to eliminate infected respiratory cells could result in excessive inflammation, so this treatment must be used in combination with other treatments, despite its many beneficial efforts.

1. Introduction

There is a global health emergency on the threat of a rapidly spreading pathogenic SARS-coronavirus 2 (SARS-CoV-2) causing COVID-19, a highly lethal pandemic of a respiratory pathogen with the potential for killing millions of people [1]. The SARS-CoV-2 pandemic presents unparalleled anti-viral treatment challenges as COVID-19 disease is inflammatory in nature and characterized by its hallmark uncontrolled inflammatory response. Therefore, the inefficiency of the immune system, both in terms of over activity and the inability to destroy the virus, can play a crucially significant role in the pathology of the virus [2]. Therefore, it is thought that inflammation reduction therapies can efficiently maintain the patient and prevent death. Based on this idea, anti-inflammatory medications have been used to reduce the severity of inflammation in some centers, including the monoclonal antibodies against inflammatory cytokines [3]. In this regard, we should not neglect the new method such as immune cell therapy to overcome therapeutic barriers. This approach was used to treat various inflammatory and autoimmune diseases such as rheumatoid arthritis (RA), and acceptable results were obtained [4,5]. Thus, this paper aims to review

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the potentially life-saving complex therapies, such as the types of immune cells that have therapeutic potential in the management of COVID-19.

2. Immunology & immunopathology of COVID-19

Although there is no exact detection of the pathogenesis of COVID-19, there are plenty of reports on the well-known mechanism (s) that is applied by the virus to the entering of host cells. SARS-CoV-2 binds to target cells through the interaction of viral spike glycoprotein (S) with the angiotensin-converting enzyme 2 (ACE2) [6] a dipeptidyl peptidase 4 (DPP4) expressed on the surface of endothelial cells [7], similar to SARS-CoV. This interaction leads to the entrance of viral RNA into the cytoplasm. Subsequently, it is encapsulated, polyadenylated, and encrypts various structural and non-structural polypeptide genes, and eventually, the novel-produced viruses are released from host cells. The released viruses infect a broad range of cells in several systems, such as respiratory, cardiovascular, renal, neurological, hepatic, biliary, reproductive, gastrointestinal, and integumentary [8]. One of the primary reasons for the prevalent symptoms of COVID-19 is the distribution of ACE2 receptors in different tissues [1]. Cellular entrance of SARS-CoV-2 hinges on the viral spike (S) protein and other viral polypeptide priming by the host cellular transmembrane serine protease 2 (TMPRSS2) in addition to the attachment of viral (S) protein to ACE2 [6]. Recent evidence from single-cell RNA sequencing (scRNA-seq) indicates that other proteases such as cathepsin B and L are more probable to be implicated in the cellular entrance procedure because both ACE2 and TMPRSS2 are not expressed on the same cell [9].

3. Immune response and cytokine storm

Hyper-inflammatory reaction to SARS-CoV-2 infection, known as cytokine release syndrome (CRS) or cytokine storm (CS), arise in some patients in whom acutely elevated serum levels of different pro-inflammatory cytokines such as interleukin (IL)-1β, IL-2, IL-6, IL-10, tumor necrosis factor-α (TNF-α), interferon-gamma (INF-γ), CXCL9, CXCL10 and soluble IL-2 receptor alpha (sIL-2Rα) are observed [1,10]. Multiple molecular pathways are proposed to better understand the complex molecular events behind the CS response in patients seriously affected by COVID-19. Understanding of the CS process is essential because it causes lymphopenia and lymphocyte dysfunction [11] and the defects in lymphocyte cytolytic activity of natural killer (NK) cells from innate immunity and CD8 cytolytic T cells from adaptive immunity are mentioned as a reason for the progress of CS [12]. However, this defective condition, either genetic or acquired, leads to the incapacity of cytolytic cells to provoke apoptosis in infected and activated antigen-presenting cells. In this sense, many pro-inflammatory cytokines are released as a result of extended and exaggerated interactions between innate and adaptive immune cells, which flow cytometry analysis demonstrates that immune cells numbers, such as $CD4^+$ T cells, $CD8^+$ T cells, NK cells, and B cells are significantly changed in a person with COVID-19 [11].

It should be noted that in the CS, both groups of pro-inflammatory and anti-inflammatory cytokines increased in patients' serum. Particularly, SARS-CoV-2 can trigger Th1 cells to secrete pro-inflammatory cytokines such as granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-6, and TNF-α, which are the principal components in the CS. Subsequently, GM-CSF produces high levels of IL-6, TNF-α, and other cytokines by activating inflammatory monocytes [13]. According to clinical evidence, the massive release of inflammatory cytokines is a potentially lethal immune situation characterized by infiltration, proliferation, and hyper-activation of heterogeneous immune cells, such as macrophages, neutrophils, NK cells, and T cells, inside the inflamed tissue [14]. The non-specific hyperactivity of immune cell infiltration results in adverse effects on tissues such as the lung. Lung failure -a common outcome of CS- causes lung-parenchyma changes, such as diffuse alveolar damage, which can develop acute lung damage or a more severe form, acute respiratory distress syndrome (ARDS), finally leading to pulmonary fibrosis and death [15]. The increase in neutrophil extracellular traps (NETs) and NETosis has been reported as a cause of CS development in COVID-19 [16]. NETs are extracellular fiber networks consisting of activated neutrophil DNA and protect against infections and pathologies of immune-mediated diseases like CS [17]. Based on autopsy findings, it is speculated that viral RNA and pro-inflammatory cytokines may stimulate neutrophils and establish NETs and NETosis. A reason for the unrestrained cytokine release is the viral manipulation of nuclear factor-kB (NF-κB) and mitogen-activated protein kinases (MAPK) signaling pathway via the Host-virus mediated TMPRSS2 and ACE2 interaction [18,19]. This interaction triggers the hyper-activation of NF-κB, predominantly in non-immune cells, including pulmonary epithelial cells, which in turn produce more cytokines and chemokines.

4. Strategies to immune cell therapy

One useful therapeutic approach may be the application of strategies for reducing the production of inflammatory cytokines. These approaches can be divided into two categories: cell-free and cell-mediated therapy. Fundamentally, the first group is applying medications, including small inhibitors such as Baricitinib, Tofacitinib, monoclonal antibodies, and secretory vesicles (known as exosomes) that contain anti-inflammatory substances. The second group, cell-mediated therapy, as the topic of this article, involves the employment of several immunomodulatory cells, which can be provided from both autologous and allogeneic sources [20]. The allogeneic source has a high priority along with the troubles, costs, and emergency conditions of COVID-19. Several immunotherapeutic approaches are currently being evaluated to combat SARS-CoV-2 infection (Table 1). These approaches are particularly focused on targeting inflammatory processes, and many other strategies are being evaluated (Fig. 1). However, in view of unpredictable immune responses in severe COVID-19 patients, all strategies based on reducing inflammation and raising the effective immune response against the SARS-CoV-2 infection considered for COVID-19 patient management are summarized in Table 1 and will be covered in more detail.

4.1. T Regulatory cells therapy

Regulatory T (Treg) cells characterized by $CD4^+CD25^{high}CD127^{low/-}FoxP3^+$ phenotypic markers, as more precise regulatory mechanisms, are naturally accessible in adjusting the initiation of adaptive immune responses and monitoring the progressive inflammation responses in the body [21]. The honored therapeutic potential of Treg cell subsets in animal models promises to elaborate novel therapeutic approaches for treating of immune-mediated diseases in humans [4]. According to the anti-inflammatory activity of Treg cells in viral pneumonia [22,23], it has been hypothesized that the disruption of Treg cells, either in quantity or function, may contribute to the severity of COVID-19 pathology [24-26]. The infiltration of these cells into the inflamed lung tissue to prevent damage can be cited as a potential reason. Decreased IL-2 and increased CD25 levels were detected in bronchoalveolar lavage specimens of patients suffering from severe COVID-19 [27,28]. Thus, a decline in IL-2 levels would stimulate Tregs apoptosis. Alternatively, COVID-19 patients have increased CD25 levels, perhaps owing to rising proteolytic degradation of CD25 cells relative to inflammation [29]. This soluble CD25 might interfere with bioavailability and signaling pathways and increase Tregs apoptosis. It should be noted that the probability of a direct SARS-CoV-2 effect on the biology of Tregs must not be ruled out because it has formerly been explained that the Middle East Respiratory Syndrome (MERS) coronavirus efficiently decreases T lymphocytes count through induction of both extrinsic and intrinsic apoptosis pathways [30]. Considering the importance of Tregs in immune homeostasis, reduction in Tregs levels could be a reason for

Table 1
Overview of cell-based clinical trials for the treatment of COVID-19.

Strategy	Type	Study Title	Phase	NCT number
Treg	–	Regulatory T Cell infusion for Lung Injury Due to COVID-19 pneumonia	1	NCT04468971
		RAPA-501-Allo Therapy of COVID-19-ARDS	1 & 2	NCT04482699
NK	NK	Clinical Trial on NK Cells for COVID-19	1	NCT04634370
		Natural Killer Cell (CYNK-001) Infusions in Adults With COVID-19	1 & 2	NCT04365101
	CAR-NK	Universal Off-the-shelf NKG2D-ACE2 CAR-NK Cells for Therapy of COVID-19	1 & 2	NCT04324996
MSC	Ad-MSCs	Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19	2	NCT04428801
	BM-MSCs	Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV)		NCT04361942
		mesenchymal Stem Cell Infusion for COVID-19 Infection	1	NCT04444271
		Mesenchymal Stem Cells Therapy in Patients With COVID-19 Pneumonia	1	NCT04713878
		mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease)	1	NCT04345601
		Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation	1	NCT04397796
	UC-MSCs	Clinical Trial of Allogeneic Mesenchymal Cells From Umbilical Cord Tissue in Patients With COVID-19	1	NCT04366271
		Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	1 & 2	NCT04339660
		Use of Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Caused by COVID-19	Early Phase 1	NCT04456361
		Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	2	NCT04288102
		Umbilical Cord-derived Mesenchymal Stem Cells for COVID-19 Patients With Acute Respiratory Distress Syndrome (ARDS)	1 & 2	NCT04355728
		Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS	1 & 2	NCT04333368
		Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome	1 & 2	NCT04400032
		Mesenchymal Stem Cells for the Treatment of COVID-19	1	NCT04573270
	NHPBSC	study Evaluating the Safety and Efficacy of Autologous Non-Hematopoietic Peripheral Blood Stem Cells in COVID-19	1 & 2	NCT04473170
	DP-MSCs	Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells	1	NCT04302519
		Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients	1 & 2	NCT04336254
	SBI-101	A Study of Cell Therapy in COVID-19 Subjects With Acute Kidney Injury Who Are Receiving Renal Replacement Therapy	1 & 2	NCT04445220
	HCT-MSCs	hCT-MSCs for COVID19 ARDS	1 & 2	NCT04399889
	HB-adMSCs	A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19	2	NCT04349631
		A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Allogeneic Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19	2	NCT04348435
	MD-MSCs	Treatment of Covid-19 Associated Pneumonia With Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells	1 & 2	NCT04382547
		Therapeutic Study to Evaluate the Safety and Efficacy of DW-MSC in COVID-19 Patients	1	NCT04535856
	Not determined	Clinical Use of Stem Cells for the Treatment of Covid-19	1 & 2	NCT04392778
		Mesenchymal Stromal Cell Therapy For The Treatment Of Acute Respiratory Distress Syndrome	1	NCT04447833
		Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019	Early Phase 1	NCT04371601
DC	–	Dendritic Cell Vaccine to Prevent COVID-19	1 & 2	NCT04685603
Specific T cell	–	Novel Adoptive Cellular Therapy With SARS-CoV-2 Specific T Cells in	1	NCT04351659

(*continued on next page*)

Table 1 (*continued*)

Strategy	Type	Study Title	Phase	NCT number
		Patients With Severe COVID-19		
		Part Two of Novel Adoptive Cellular Therapy With SARS-CoV-2 Specific T Cells in Patients With Severe COVID-19	1 &2	NCT04457726
		SARS-CoV-2 Specific Cytotoxic T Lymphocytes for the Treatment of COVID-19 in Patients With Cancer	1	NCT04742595
memory T and B cell	–	COVID-19: SARS-CoV-2 Specific Memory B and T-$CD4^{\pm}$ Cells		NCT04402892
		Safety Infusion of Natural Killer cells or Memory T Cells as Adoptive Therapy in COVID-19 pneumonia or Lymphopenia	1 &2	NCT04578210
monocyte	–	The MONACO Cell Therapy Study: Monocytes as an Anti-fibrotic Treatment After COVID-19	1 &2	NCT04805086

Dental pulp: DP
Non-hematopoietic peripheral blood stem cells: NHPBSC
Mucosa-derived Mesenchymal Stem Cells: MD-MSCs
Allogeneic hybrid Treg/Th2 cell (RAPA-501-ALLO)
Human cord tissue mesenchymal stromal cells: HC-MSCs
Hope biosciences autologous mesenchymal stem cell: HB-adMSCs

the overstimulation of the immune system and lung damage in severe COVID-19 patients. Therefore, the potential of regenerating either the quantity or function of these cells in patients has been proposed [31]. Noted that some factors like obesity or chronic diseases like systemic lupus erythematosus (SLE) and diabetes are the risk factors for COVID-19, and data from these subjects indicate that Tregs quantity or activity reduced compared with those in healthy subjects, and, so, there is a higher state of inflammation and CS.

The revival of Treg cell function has been markedly reported after the administration of biological medication in patients with an inflammatory disease like RA [32], albeit those medications are not primarily designed with the intention of adjusting Treg cells. Hence, multiple approaches have been devised to enhance the quantity and recover the function of Treg cells, such as the expansion of autologous Treg, expansion of antigen-specific Treg, induced Treg from the naïve $CD4^{+}$ T cell, and FoxP3 gene transduction [33-35]. The available evidence for Treg cell potential in therapy can be outlined in two sections, covering both *in vivo* and *ex vivo* evidence. Adoptive transfusion of Treg cells in respiratory syncytial virus-infected animals reduces immunopathology by regulating the $CD8^{+}$ effector T cells against the virus [36]. Additionally, to inhibit inflammatory responses, Treg cells can enhance tissue remediation by the expression of amphiregulin, which does not depend on the immunosuppressive activity of Treg cells [37].

4.2. Natural killer cell therapy

Natural killer (NK) cells, as a part of the innate immune system, serve as useful effectors against life-threatening viral infection. The results indicate a correlation between a higher count of NK cells in peripheral blood with negative viral RNA and positive IgG/IgM tests [38]. The assessment of SARS-CoV-2 and SARS-CoV-1 clinical data shows that COVID-19 disease severity is correlated with a greater reduction in the count of NK cells [39], the exhaustion of NK cells, lack of specific maturity, and potent NK cell phenotypes [40]. However, the NK cell lymphocytopenia group had a remarkably worse survival ratio and a long period of viral shedding. Because NK cells play an essential role against SARS-CoV-2-infected cells in several manners, including the direct killing effect through killer-cell immunoglobulin-like receptors (KIR) receptors mediated apoptosis, degranulation, antibody-dependent cell-mediated cytotoxicity (ADCC), active interaction with dendritic cells (DC) in antigen presentation processes and the secretion of specific cytokines.

Notably, these anti-viral properties make NK cells more useful candidates for any pandemic infections and re-emerging viruses, as well as COVID-19 immunotherapy. Several publications have mentioned a potential role of NK cells in fighting various viral infections, as well as COVID-19 with a permanent modification in the NK cell profile toward those more mature and potent phenotypes in recovering patients [41-44]. Early adoptive transfer of highly activated NK cells at the onset of the disease may encourage innate and adaptive immunity, thereby improving survival and reducing rates of disease progression in SARS-CoV-2 infected patients.

4.3. Mesenchymal stem cells therapy

The therapeutic application of mesenchymal stem cells (MSCs) as a promising prospect has been extensively investigated for various clinical applications in medicine. There are two hypotheses based on their unique characteristics -immunomodulatory and regenerative potencies- that comprise: 1) they can reduce acute lung damage and 2) they can suppress severe cellular inflammatory responses induced by SARS-CoV-2. Therefore, these multipotent cells may be exploited in various branches of therapy, which includes regenerative medicine, immunotherapy, tissue engineering, and cellular / molecular biology [45-48]. The immunomodulatory activities of MSCs would possibly consist of (a) inhibiting the proliferation and function of T cells, B cells, DCs, and NK cells; (b) polarizing monocytes to anti-inflammatory M2 macrophages; (c) producing IL-10 associate with diminishing the production of TNF-α and IL-12 and (d) inhibiting the production of hydrogen peroxide by stimulated neutrophils [49-52]. Moreover, MSCs have potent anti-fibrotic effects and decrease lung fibrosis [53,54], which facilitates the regeneration of damaged pulmonary epithelial cells and promotes alveolar fluid clearance [11]. Hence, lung function is renovated through augmented alveolar air-space volume, reducing alveolar thickening, and inflammation markers [55,56].

Unlike different cells, MSCs do not substantially express the surface ACE2 receptor and TMPRSS2 receptors (entrance gate of coronavirus into the host cells), which ensures that adoptive MSCs transfer therapy can perform their immunomodulatory effects without being neither infected nor destroyed by the virus [57]. Moreover, intrinsic interferon-stimulated genes (ISGs) play a significant role in MSCs' resistance to viral infections as compared to their differentiated progenies. In fact, viral infection is prevented by the expression of ISGs [58]. Additionally, the produced Leukemia inhibitory factor (LIF) by MSCs has the capacity to neutralize CS in the lungs during viral pneumonia [59]. Moreover, several studies indicated that some antiviral activities of the MSCs contributed to the expression of indoleamine-pyrrole 2,3-dioxygenase (IDO) by these cells [60-62]. The apoptosis of activated T cells and the transformation of tryptophan into kynurenine are induced by the secretion of IDO from MSCs, which suppresses the proliferation of effector T cells [63]. MSCs also contribute to the protection of both epithelial and endothelial barrier function in ARDS and sepsis [64,65]. Due to the pathogenesis of ARDS, the restoration of disrupted alveolar-capillary barrier is promoted by keratinocytes growth factor (KGF) and angiopoietin-1 (Ang-1) secreted by MSCs [66]. It is beneficial for patients who develop pulmonary fibrosis even after surviving the acute phase of the disease [67-69].

In comparison with other sources of MSCs, umbilical cord mesenchymal stem cells (UC-MSCs) have been predominantly exploited in diverse diseases because of their adequate collection, no ethical issues, little immunogenicity, and rapid proliferation rate [70,71]. An

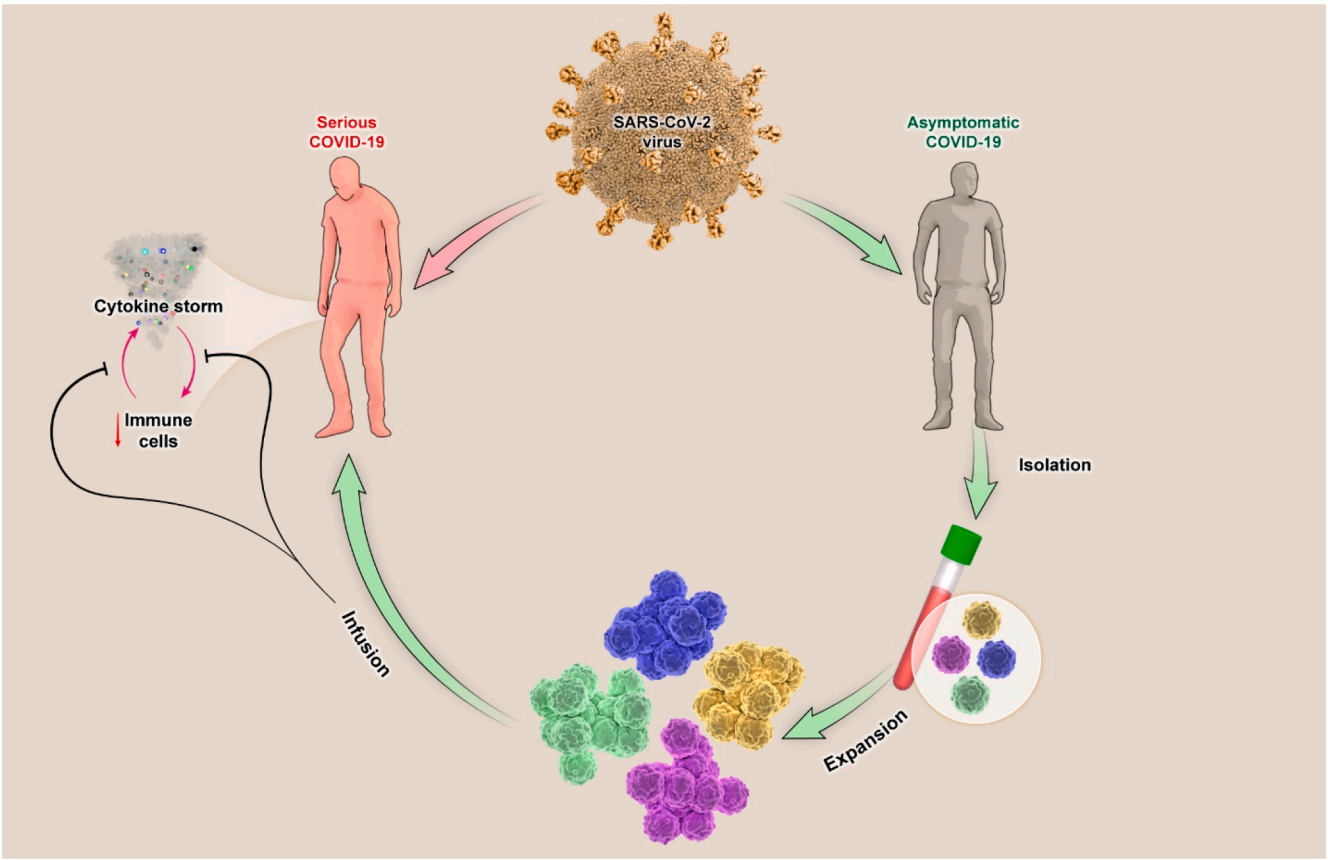

Fig. 1. Schematically strategy for Immune Cell-Based Immunotherapy 19. In immunotherapy, the first step is to mass-produce functional immune cells that can be from recovered individuals and subsequently re-injected to the severely affected patient after performing of expansion procedures *in vitro*. Injected immune cells, relying on their functional properties, can suppress the process of cytokine storm and reduction of immune cells that results in improving the patient with severe symptoms.

established route of treatment with UC-MSCs is the intravenous injection of these cells as they are trapped in the lungs, the most affected organ in COVID-19 patients [72], but it is still unknown whether the intratracheal / bronchial administration of MSCs is feasible and efficient or not [73]. The average size of MSCs is about 30 μm (range 16 to 53 μm), which range is in the relatively large cells category [74,75]. Hence, after intravenous administration, they are merely trapped in the lungs and are beneficial for COVID-19 therapy because viruses, particularly targeting this organ, might be a priority to other therapies [76]. Modulation of immune cells activation, suppression of infiltrating cells, and reduction of edema can contribute to the regulation of the immune system in the lung tissue by these cells [77]. According to reviews of the function of extracellular vesicles (EVs), including microvesicles and exosomes, MSCs may be effective in healing acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) by producing EVs [11,78]. In a clinical survey of patients infected with the H7N9 influenza virus, which submitted symptoms such as ARDS, lung failure, and severe pneumonia, MSC post-transplant mortality rate has decreased without adverse effects [79]. Since influenza A and COVID-19 share related symptoms (such as ARDS and lung failure) and similar multi-organ dysfunction, MSC-based therapy may be a promising alternative therapy to deal with COVID-19.

4.4. Dendritic cells therapy

Dendritic cells (DCs) with various subpopulations, as well known as conventional dendritic cells (cDCs) and plasmacytoid dendritic cells (pDCs), play a critical role in both innate and adaptive immune responses against pathogens. Simultaneously, it also provides an essential service for effective vaccination. Furthermore, activated DCs could save the adjacent cells from viral attack through the secretion of a considerable level of type one interferons [80]. It should be regarded that in the case of SARS-CoV-2 infection, DCs infected along with endothelial cells like type II alveolar, and infected DCs might assist the induction of CS in patients [81]. Inquiry of DCs in COVID-19 patients has proved depletion and reduction of maturation in both cDC and pDC subsets and a re-localization of activated cDC2 in the lungs [82,83]. Prior findings stated the inadequacy of T-cell responses to the virus and induction of NK cell cytotoxicity against infected DCs owing to downregulation of MHC-I and II molecules as well as a decreased expression of CD80/CD86 molecules on MERS- infected DCs. [83,84]. According to the T cell insufficiency in COVID-19 patients and the vital role of DCs in T cell priming, it seems reasonable to reinforce DCs for activating vigorous T cell responses in these patients. It has already been established that antigen-specific T cell responses stimulated by DC-delivered peptides are 100 to 1000 fold more effective than nonspecific stimulation [85]. Therefore, there are great attempts to induce efficient immune responses using DCs presenting specific viral antigens in severe infections such as human immunodeficiency virus (HIV) [5]. For the intent of DC therapy, there are two main cell sources, including $CD14^{+}$ monocytes from peripheral blood mononuclear cells (PBMCs) and the $CD34^{+}$ stem cells from the umbilical cord or bone marrow. Although the application of these cells in anti-cancer DC-based therapy has given encouraging results [86], a serious concern in using DCs to treat COVID-19 is the potential of *in-vivo* differentiation to the inflammatory macrophages. As noted, macrophages are one of the major sources of pro-inflammatory cytokines secretion and pernicious inflammation inside the infected tissue.

The other limitation in the autologous $CD14^+$ cells assembly pathway is the high risk of extracting infected monocytes whose function was formerly impaired [87]. To defeat problems, $CD34^+$ stem cells can be exploited after differentiation into DCs in the presence of GM-CSF *in vitro*. In this sense, umbilical cord stem cells appear to be preferable because they generate a milder graft- versus-host-disease (GVHD) and require less HLA matching between donor and recipient; however, bone marrow-derived cells possessing immunomodulatory properties provide further gains for the patients suffering from disordered cytokine production [88]. There are other questions that need to be responded in DC-based therapy. To achieve the most advantages of DCs function, they should be loaded with appropriate antigens that could trigger preferentially antigen-specific T cell responses against the viral particles. Obviously, an excellent candidate for this purpose is the spike protein (S) of SARS-CoV. The constructed-S protein was explained to induce both cellular and antibody-mediated responses. Nevertheless, determining the best peptide fragments derived from this huge protein is a subject still under investigation. Several supplied structural epitopes and peptide fragments of SARS-CoV, which are presumed to activate antiviral cytotoxic T cells, comprise; S_{436}, S_{525}, EP1 (aa 51–71), EP2 (aa 134–208), EP3 (aa 249–273), EP4 (aa 349–422), and N1 from the N protein [89,90]. $S_{450\text{-}650}$ is another fragment under survey that is believed to provoke appreciable antigen-specific responses; nonetheless, the conformational multiplicity makes it more complex to ascertain a suitable peptide that could induce the production of reliable T-dependent neutralizing antibodies [91]. After choosing the best antigen, the next step is to select the most convenient antigen-loading technique. There are several introduced ways, including; RNA injection by electroporation, lipid-mediated transfection, viral vectors, and antigen nanoparticles [92,93]. Some investigators have also attempted to differentiate monocytes into DCs using extracorporeal photopheresis (ECP) and prime them with killed viruses to develop potent DCs [94]. Although the antigen loading techniques are continuously improving, some disadvantages such as toxicity, allergenicity, and the possibility of DC phenotype alteration remain to be worked out. Besides all these efforts to generate efficient DCs for inducing T-cell responses against coronavirus, it is worth remarking that generation of tolerogenic DCs with andrographolide, which prevents NF-KB, might help control the excessive immune responses in COVID-19 patients [84].

4.5. Chimeric antigen receptor T cell therapy

Chimeric antigen receptor (CAR) and T cell receptor (TCR) T-cell therapy involve genetically modified patient's T-cells with antigen-specific receptors. This approach, as a revolution in anti-cancer immunotherapy, is a reviving therapy in handling different types of cancer. Based on the ability of CAR-T and TCR-T cells to recognize specific surface and intracellular antigens, respectively, and guide the immune cells to eradicate the targets when infused back into the patients, the harnessing potency of these approaches have been proposed to treat viral infections such as hepatitis B and HIV beyond cancer [95]. Therefore, scientists are investigating the adoptive transfer of SARS-CoV-2 − specific T-cells to prevent and treat COVID-19, based on previous research in which the developed SARS-specific cytotoxic T-cells conducted by specific-TCR gene transfer could recognize SARS antigens [96].

Even though CAR-T or TCR-T therapy has provided an inimitable response, there are several potential disadvantages that must be considered and overcome, including long-lasting cytopenia, CS, neurotoxicity, and elimination of all infected cells that might affect vital organs [97-100]. One way to address this dilemma is to engineer CAR/TCR T-cells using mRNA electroporation, which can restrict their functional activity duration and inflammatory capability [96]. Furthermore, it is undoubtedly offered that combination therapy - CAR/TCR T-cells combined with an anti-viral medication may prove to be safe and effective. Generally, focused and rigorous research is necessary to refine the immunotherapy approach to treating COVID-19 and other viral diseases.

4.6. Specific T cell therapy

Cellular immunity, particularly specific-memory T cells, has gained a special interest in the induction of sustained immunity against coronaviruses, involving unstable antibody-mediated immunity in convalescent patients and reducing IgM and IgG serum levels against coronavirus antigens [101]. It has already been found that virus-specific T cells could be isolated and expanded. These T cells are able to recognize various viral antigens, especially structural antigens such as membrane proteins [102]. In a recent study, SARS-CoV-2-specific T cells (SARS-CoV-STs) were isolated from PBMCs of convalescent donors and cultured in the presence of IL-4 and IL-7. ELISPOT analysis indicated that these T cells could respond to the membrane, spike, and nucleocapsid proteins. The results also suggest the potential of specific-T cell therapy, either from an autologous or off-the-shelf source, to treat critical COVID-19 patients and gives hope for preventive strategies in case of immunocompromised patients such as those undergoing hematopoietic stem cell transplantation [103]. Currently, two clinical trials are investigating SARS-CoV-STs therapy, which follows three major goals, including the feasibility of rapidly isolating SARS-CoV-STs from the convalescent donors, appropriately using SARS-CoV-2-specific peptides and an automated medical device for the emerging therapy for severe COVID-19.

5. General and fundamental aspects of cell therapy efficacy

The main aim of cell therapy is to reinvigorate the patient's diminished and failed immune system. This aim might be out of achieving or ineffective owing to the production of elevated levels of inflammatory cytokines along with altered expression of immunosuppressive agents. The normal immune system is skilled at maintaining immune tolerance and preventing autoimmunity by expressing immune checkpoint molecules and silencing the effector T cell function [104]. In this regard, plenty of pathogens as well as cancer cells induced the expression of immune checkpoint molecules to escape the host's immune surveillance, which leads to the effector T cell exhaustion [105,106]. Since immune cell therapy has been alternatively proposed as a high-potential therapy for COVID-19 patients, it is substantial that health care providers have a definite insight into the advantages and disadvantages of cell therapy. Therefore, the application of immune checkpoint inhibitors (ICIs) before or during cell therapy might be considered as an appropriate combination therapy method to treat and/or improve the outcome of chronic and acute infectious diseases treatment [105].

6. The application of immune checkpoint inhibitors

Immune checkpoints express naturally throughout the immune system and are principally responsible for modulating immune response [105]. These molecules are triggered after binding to relevant ligands on the surface of other cells and launch an immunosuppressive message to the immune cell, which ultimately provides the essential equilibrium of both co-stimulatory and co-inhibitory signals in T cell activation [105]. As an escape mechanism and overcoming the host immune response, SARS-CoV-2 uses diverse procedures similar to other infectious agents or cancer cells. A clear example is a SARS-CoV-2 ability to produce severe leukopenia through the production of PLpro and ORF3b, which prevents NF-κB cleavage from IkBα and IRF3 nuclear localization, respectively. SARS-CoV-2 infection, in addition to the reduction of T cells, increases the exhaustion of effector T cells by provoking the expression of inhibitory receptors such as programmable cell death protein-1 (PD-1), T-cell immunoglobulin and mucin domain-3 (TIM-3), and T cell immune receptor with Ig and ITIM domains (TIGIT) on the surface of immune cells, such as T cells, consequently evolving of CS or by reducing the regulatory T cell population [106-109]. According to the reported results, *in*

vitro blockade of PD-1 improves T cell function and enhances T cell-mediated response to SARS-CoV-2 peptides [110].

The ICIs are monoclonal antibodies that are used to recover cell-mediated immunocompetence [111] through targeting T-cell exhaustion pathways [112], interrupting the binding of immune checkpoint proteins to their ligands [113]. The main classes of ICIs containing anti-PD-1, anti-Programmed death-ligand 1 (PD-L1), and anti-cytotoxic T lymphocyte-associated protein (CTLA-4) antibodies have been potentially planned for managing as immunotherapy medicine in solid tumors [105,106] can enhance the immune response in COVID-19 patients [111,113]. Although the application of ICIs-containing therapy regimens may have indicated constructive results in some research, it is essential to remark that a higher rate of hospitalization was observed among patients receiving ICIs-containing regimens. Because of immunotherapy-induced pneumonitis, their application as an effective medicine is in an ambiguous state [112,114,115]. Nevertheless, there are currently four clinical trials to evaluate the effectiveness of anti-PD-1 antibody administration for cancer and non-cancer patients with COVID-19 [113].

7. Conclusion

Since the outbreak of COVID-19, we have witnessed a new wave of morbidity and mortality owing to the incidence of COVID-19 in the community continuing to rise. Therefore, given the many impediments to the vaccination process and the mutations that occur in the viral genome, the introduction of an approved treatment method remains an urgent medical need. It appears that the COVID-19 treatment is likely to demand an effective strategy to modulate the over-activation of the immune system while increasing its ability to destroy the virus. Although many ambiguities remain unclear about the application of immune cell therapy, their massive capacity to induce immune homeostasis and biological tolerance makes them a perfect target for any therapeutic application. Hence, we focused on providing insight into the potential benefits of immune-cell therapy in the COVID-19 treatment. Obtained promising findings and technological advances result in improving new therapeutic possibilities, which are favored by both immune system disorders and regenerative medicine. Various immunotherapy approaches that block CS, further lung damage and help to regenerate lung tissue have gained massive attention in the management of patients with severe COVID-19. Meanwhile, the MSC-based approaches appear to be extra attractive to overcome COVID-19, given that it has been the subject of vast clinical studies. Finally, accurate management of immune response in any way that stimulates antiviral immunity while suppressing systemic inflammation could be the key to success in COVID-19 treatment. We therefore, suggest that the combination of cell-based therapy and other therapies is a worthy field for further investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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