An overview of the recent findings of cell-based therapies for the treatment and management of COVID-19

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ABSTRACT

The coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic taking the lives of millions. The virus itself not only invades and destroys the angiotensin-converting enzyme 2 (ACE2)-expressing cells of the lungs, kidneys, liver, *etc.* but also elicits a hyperinflammatory immune response, further damaging the tissue leading to acute respiratory distress syndrome (ARDS) and death. Although vaccines, as a prime example of active immunotherapy, have clearly disrupted the transmission of virus and reduced mortality, hospitalization, and burden of disease, other avenues of immunotherapy are also being explored. One such approach would be to adoptively transfer modified/unmodified immune cells to the critically ill. Here, we compiled and summarized the immunopathogenesis of SARS-CoV-2 and the recent preclinical and clinical data on the potential of cell-based therapies in the fight against COVID-19.

1. Introduction

In December 2019, a type of contagious pneumonia was reported in Wuhan, China which was later called the coronavirus disease-19 (COVID-19). One major symptom of the disease was severe acute respiratory syndrome (SARS), and it was caused by a species of the Coronaviridae family [1]. Hence, the virus that rapidly swept across the globe with a pandemic of magnificent proportions was named SARS-CoV-2. Before COVID-19, SARS-CoV and the Middle East respiratory syndrome (MERS)-CoV were the other outbreaks caused by the Coronaviridae family, but none had the global impact that COVID-19 demonstrated [2]. SARS-CoV-2 has more than 80% genomic similarity to that of SARS-CoV, and using the spike (S) glycoproteins of its receptor-binding domains (RBDs) invades the type II alveolar epithelial cells through angiotensin-converting enzyme 2 (ACE2) with high affinity, which might explain why SARS-CoV-2 is highly contagious [3].

Needless to say, the impact of COVID-19 worldwide has prompted the need for developing vaccines and therapies. Immunotherapy seeks to harness the strength of the immune system to fend off pathogens. Most of the current therapies for COVID-19 emphasize the active aspect of immunotherapy, such as the use of vaccines. While many of the vaccines approved through Emergency Use Authorization (EUA) have proved an efficacy of greater than 70%, they have raised some concerns as well, which include the yet-unknown durability of the immune response, no immunity in the upper respiratory tract, and failure in high viral load [4]. In such cases, all therapeutic options must be scrutinized, including adoptive immunotherapy, a form of passive immunotherapy which takes advantage of the cells of the immune system to counter the infection [5]. Some subtypes of adoptive cell therapy, such as dendritic cells (DCs), can also be categorized as vaccine therapy [6]. Here, we focus on the feasibility and efficacy of using the immune cells as treatments for COVID-19.

2. A prelude to COVID-19 immunopathogenesis and immune cell responses against SARS-CoV-2 infection

The SARS-CoV-2 virus is distributed through tiny droplets from infected patients. Then, the virus replicates in the lungs and progresses

to the lower airway tracts. The immune response is key in defining the outcome of the disease. The primary infection evokes a local immune response which is commenced by innate immunity. The antigen-presenting cells (APCs) such as macrophages and DCs recognize and present the immune cells with pathogen-associated molecular patterns (PAMPs) of the virus to induce a biological response. Natural killer (NK) cells exert their function in the absence of an APC. This immune response culminates in the secretion of chemokines and cytokines such as IL-12, IL-6, IFN-γ, TNF-α, monocyte chemoattractant protein (MCP-1), and IL-1β [7]. Activated APCs also secrete type I IFNs and inflammatory cytokines which galvanize NK cells of the innate immunity and the cells of the adaptive immunity. These cytokines signal the attraction of neutrophils, macrophages/monocytes, and lymphocytes to the infection site to clear the virus (Fig. 1).

Adaptive immunity initiates when CD4+ helper T-cells (Th) are presented with virus antigens by APCs. Upon stimulation, Th1 cells secrete IL-2, IFN-γ, and TNF-α to activate cytotoxic T-cells (CTLs), a major defense mechanism versus SARS-CoV-2. The humoral aspect of adaptive immunity is governed by Th2 stimulation of B-cells to secrete

neutralizing antibodies (short-lasting IgM and long-lasting IgG) after differentiating to plasma cells and memory B cells [8]. The formation of memory T cells is another favorable byproduct of the activation of adaptive immunity, which was previously shown to persist for up to four years after initial exposure to SARS-CoV [9]. In another follow-up study, memory T cells were present six years after recovery, while Ag-specific memory B cells and SARS-CoV IgG were not detected in SARS-CoV recovered patients after six years [10]. This makes looking into T cell-based therapies for the novel SARS-CoV-2 all the more expedient.

Besides the high levels of inflammatory markers, such as ferritin, C-reactive protein (CRP), and D-dimer, lymphopenia, basopenia, and eosinopenia are common features of SARS-CoV-2 infection and are correlated with disease severity [11]. Lymphocytopenia is mostly due to reduced NK cell, B cell, and most importantly T cell numbers. This could be due to direct virus toxicity and infiltration and sequestration of lymphocytes in lung tissue or indirect factors such as diabetes and hypertension [12]. Th17 would be an exception since its inflammatory cytokines exacerbate the pathogenesis of COVID-19. Although T cells secrete activation cytokines, such as IL-2, TNF-α, and IFN-γ and express
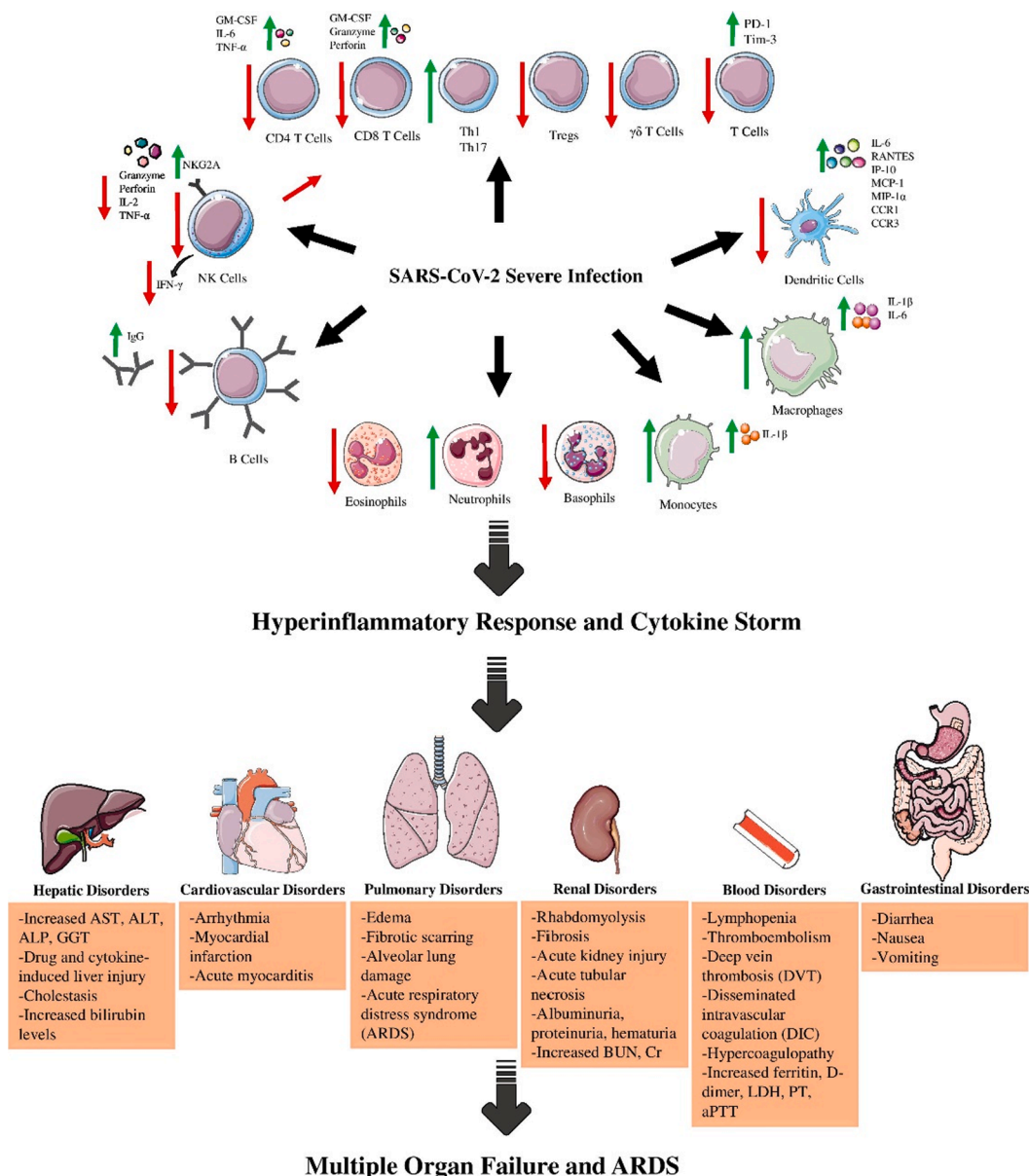

Fig. 1. the diagram depicting the process of ARDS creation. Over-activation of the immune cells results in cytokine storm and deleterious effects on organs such as lungs, gastrointestinal system, kidneys, etc. (Figure illustrated with the help of https://smart.servier.com/).

Table 1

Active clinical trials using T cells, DC vaccines, NK cells, and MSCs in COVID-19 treatment. Data extracted from https://clinicaltrials.gov/ (last accessed 9/15/2021).

Treatment	Phase	Drug	Explanation/intervention	Country	NCT number
NK cell	I/II	CYNK-001	To assess the safety of NK cells derived from human placental CD34 + stem cells as a treatment option	USA	NCT04365101
	I	NK cells/ conventional therapy	To assess the safety of NK cells plus conventional therapy in COVID-19 patients	China	NCT04280224
	I	FT516	To assess the safety of off-the-shelf iPSC-derived NK cells	USA	NCT04363346
	I	DVX201	To assess the safety of NK cells derived from CD34 + hematopoietic stem cells	USA	NCT04900454
	I	NK cells	To assess the safety of ex vivo expanded NK cells	Brazil	NCT04634370
	I/II	NK cells/ T cells	To assess the safety of NK cells and memory T cells from convalescent donors	Spain	NCT04578210
	I/II	NKG2D-ACE2 CAR-NK Cells	To assess the safety of IL15 superagonist- and GM-CSF neutralizing scFv-secreting NKG2D-ACE2 CAR-NK derived from cord blood	China	NCT04324996
	I	agenT-797	To assess the safety and efficacy of an unmodified, allogeneic iNKT therapy in ARDS patients	USA	NCT04582201
DC	I/II	AV-COVID-19	To assess the safety of monocyte-derived autologous DCs loaded with spike protein	USA	NCT04386252
	I	DC Vaccine	To assess the safety of minigene-containing DC vaccine	China	NCT04299724
	I/II	Minigene Vaccine/ CTLs	Minigene-containing LV-SMENP-DC vaccine plus antigen-specific CTLs	China	NCT04276896
	I	AV-COVID-19	To assess the safety of autologous DCs loaded with spike protein with or without GM-CSF	Indonesia	NCT04690387
	I	AV-COVID-19	To assess the safety of autologous DCs loaded with spike protein with or without GM-CSF	Indonesia	NCT04685603
T cell	I	CSTC-Exo	Exosomes of SARS-CoV-2-specific T cells	Turkey	NCT04389385
	–	VSTs	To assess the possibility of VST production from convalescent donors	Singapore	NCT04351659
	I/II	VSTs	To assess the possibility of VST production from convalescent donors and its safety as a treatment	Singapore	NCT04457726
	I	VSTs	To assess the safety of partially HLA-matched VSTs as a treatment option	USA	NCT04401410
	I/II	IMP	To assess the safety of VSTs as a treatment option at various doses	Germany	NCT04762186
	I	VSTs	To assess the safety of HLA-matched CTLs	USA	NCT04742595
	I	VSTs	To assess the safety of CTLs as a treatment	USA	NCT04765449
	I/II	TCB008	To assess the safety of γδ T cells of unrelated donors as a treatment	UK	NCT04834128
	I	CK0802	Treatment of ARDS using cord blood derived regulatory T cells	USA	NCT04468971
	I/II	RAPA-501-ALLO	Off-the-shelf allogeneic hybrid Treg/Th2 Cells	USA	NCT04482699
	I/II	AlloStim	Allogenic memory T cells	USA	NCT04441047
MSC	II	Secretome-MSC	Injection of isolated S-MSCs from culture medium	Indonesia	NCT04753476
	I	ExoFlo™	Injection of bone marrow MSCs' extracellular vesicles to alleviate ARDS	USA	NCT04657458
	II	EXIT-COVID19	Injection of bone marrow MSCs' extracellular vesicles to alleviate ARDS	USA	NCT04493242
	I	MSC exosome	Inhalation of MSC-derived secretomes to treat COVID-19 pneumonia	China	NCT04276987
	II	MSCs	Injection of MSCs for the treatment of ARDS	Mexico	NCT04416139
	I/II	MSCs	Injection of allogenic pooled olfactory mucosa-derived MSCs	Belarus	NCT04382547
	I/II	MSCs	Injection of human dental pulp-derived MSCs to treat ARDS	China	NCT04336254
	I	MSCs	Injection of umbilical cord-derived MSCs to alleviate COVID-19 pneumonia	USA	NCT04490486
	I/II	Astrostem-V	Injection of allogeneic adipose tissue-derived MSCs to control ARDS	South Korea	NCT04527224
	II	MSCs	Injection of adipose tissue-derived MSCs to control ARDS		NCT04905836
	II	MSCs	Injection of autologous adipose tissue-derived MSCs to control ARDS	USA	NCT04428801
	I	MSCs	Injection of Wharton's Jelly MSCs for treatment of COVID-19 ARDS	Jordan	NCT04313322
	I	MSCs	Ascertain the positive effects of MSC injection on DNA repair genes		NCT04898088
	II	NestaCell®	Assess the efficacy of NestaCell® in combination with conventional therapy	Brazil	NCT04315987
	I/II	MSCs	Injection of bone marrow-derived MSCs to treat ARDS	China	NCT04346368
	II	MSCs	Injection of MSCs to treat COVID-19-associated pneumonia	Spain	NCT04361942
	II	MSCs	Injection of bone marrow-derived MSCs to treat COVID-19-associated pneumonia	Pakistan	NCT04444271
	I	MSCs	Investigate the safety of allogenic MSC injection	Brazil	NCT04467047
	I/II	MSCs	Injection of MSCs to treat ARDS	USA	NCT04345601
	I/II	MSCs	Injection of umbilical cord-derived MSCs to alleviate COVID-19 pneumonia	Canada	NCT04400032
	I/II	MSCs	Injection of cord blood-derived MSCs to alleviate COVID-19 pneumonia	USA	NCT04565665
	I	PSC-04	To assess the safety of allogeneic adipose-derived MSCs	USA	NCT04486001
	II	MSCs	To assess the safety of umbilical cord-derived MSCs	Colombia	NCT04429763
	I	MSCs	Injection of Wharton Jelly-derived MSCs to treat ARDS	Mexico	NCT04456361
	I/II	MSCs	Injection of Wharton Jelly-derived MSCs to treat ARDS	France	NCT04625738
	I/II	MSCs	Injection of human cord tissue MSCs to treat ARDS	USA	NCT04399889
	II	MSCs	Injection of MSCs to treat ARDS	Spain	NCT04615429
	I/II	MSCs	To assess the safety and efficacy of allogeneic, adipose tissue-derived MSCs to alleviate COVID-19 pneumonia	Spain	NCT04366323
	I	MSCs	Injection of Longeveron MSCs to treat COVID-19 and Flu-elicited ARDS	USA	NCT04629105
	I	ADR-001	To assess the safety and efficacy of adipose tissue-derived MSCs to alleviate COVID-19 pneumonia	Japan	NCT04522986
	I	MSCs	Injection of dental pulp MSCs to treat ARDS	China	NCT04302519
	II	MSCs	Multiple dosing of MSC as a treatment study for COVID-19 ARDS	USA	NCT04466098
	I	MSCs	Injection of human cord tissue MSCs to treat ARDS	Brazil	NCT04525378
	I	MSCs	Injection of autologous adipose tissue-derived MSCs to control ARDS	USA	NCT04352803
	I/II	MSCs	Injection of Wharton's Jelly MSCs for treatment of COVID-19 ARDS	Colombia	NCT04390152
	II	MSCs	To assess the efficacy of MSC injection in COVID-19 patients	Pakistan	NCT04437823
	II	MSCs	Injection of umbilical cord-derived MSCs to alleviate COVID-19 pneumonia	China	NCT04288102
	I	DW-MSCs	To assess the safety and efficacy of MSC injection in COVID-19 patients	Indonesia	NCT04535856
	I	MSCs	Injection of umbilical cord-derived MSCs to alleviate COVID-19 pneumonia	Indonesia	NCT04457609
	I/II	MSCs	Injection of umbilical cord-derived MSCs to alleviate COVID-19 pneumonia	China	NCT04339660
	I	MSCs	To assess the safety of umbilical cord-derived MSCs in COVID-19 patients	China	NCT04273646
	I/II	MSCs	To assess the safety and efficacy of MSC therapy	Belgium	NCT04445454
	I/II	SBI-101	To assess the safety of MSC therapy in COVID-19 patients with acute kidney injury	USA	NCT04445220

Table 1 (*continued*)

Treatment	Phase	Drug	Explanation/intervention	Country	NCT number
	I	MSCs	Injection of MSCs to alleviate COVID-19 pneumonia	Mexico	NCT04611256
	I/II	MSCs	Injection of umbilical cord-derived MSCs to alleviate COVID-19 ARDS	USA	NCT04355728
	I	MSCs	Injection of MSCs to alleviate COVID-19 pneumonia	China	NCT04252118
	II	HB-adMSCs	Injection of allogeneic adipose-derived MSCs to provide support against COVID-19	USA	NCT04348435
	II	HB-adMSCs	Injection of allogeneic adipose-derived MSCs to provide support against COVID-19	USA	NCT04349631
	I	MSCs	To assess the safety of MSC therapy in COVID-19 patients	China	NCT04371601
	I/II	MSCs	Injection of umbilical cord-derived MSCs to alleviate COVID-19 ARDS	France	NCT04333368
	I/II	MSCs	Injection of MSCs to alleviate COVID-19 pneumonia and multiple organ failure	Turkey	NCT04392778
	I/II	XCEL-UMC-BETA	To assess the safety and efficacy of MSC therapy	Spain	NCT04390139
	I	PrimePro	To assess the palliative effects of MSC administration in COVID-19 patients and as prophylaxis in healthcare providers	USA	NCT04573270
	I/II	MSCs	Injection of allogeneic cryopreserved umbilical cord- and placenta-derived MSCs to alleviate COVID-19 ARDS	Ukraine	NCT04461925
	II	PLX-PAD	To assess the efficacy of MSC therapy	USA	NCT04389450
	II	HB-adMSC	To assess the efficacy and safety of allogeneic adipose-derived MSCs	USA	NCT04362189
	I	BM-Allo.MSC	To assess the safety of allogeneic bone marrow-derived MSC therapy	USA	NCT04397796
	I/II	BX-U001	Injection of umbilical cord-derived MSCs to alleviate COVID-19 ARDS	USA	NCT04452097
	I/II	CYP-001	To assess the safety of MSC injection in ICU patients with respiratory failure	Australia	NCT04537351
	II	PLX-PAD	To assess the efficacy of MSC therapy	Germany	NCT04614025
	I/II	MSCs	Injection of umbilical cord derived CD362 enriched MSCs to alleviate COVID-19 ARDS	UK	NCT03042143
	II	MSCs	Injection of bone marrow-derived MSCs to treat ARDS	Germany	NCT04377334
	III	Remestemcel-L	To assess the safety and efficacy of MSC plus standard care in ARDS patients	USA	NCT04371393
	II	MSC	Injection of umbilical cord-derived MSCs to alleviate COVID-19 ARDS	China	NCT04269525
	I/II	ACT-20-MSC/ACT-20-CM	To assess the safety and efficacy of umbilical cord-derived MSC in ARDS patients	USA	NCT04398303

MSC: mesenchymal stromal cell; NK cell: natural killer cell; iPSC: induced pluripotent stem cell; CAR: chimeric antigen receptor; DC: dendritic cell; CTL: cytotoxic T cell; GM-CSF; granulocyte monocyte colony-stimulating factor; VST: virus-specific T cell; ARDS: acute respiratory distress syndrome; HLA: human leukocyte antigen

Dendritic Cells

-Can be pulsed and activated ex vivo with the spike protein and reinfused back into patient to activate lymphocytes
-Can be forced to constitutively express spike gene using gene vectors
-Can be used in combination with cytotoxic T cells

T Cells

-Virus-specific T cells (VSTs), memory T cells and γδ T cells can be isolated from convalescent donors, expanded and injected to patients
-VST exosomes are a viable treatment option
-Tregs can ameliorate inflammatory response
-Gene-editing can be used to boost T cell immune functions

Mesenchymal Stem Cells

-Have immunomodulatory effects
-Possess Low MHC-I expression
-MSC exosomes also have regenerative effects
-MSC exosomes lack MHC-I expression as well
-Exosomes can be inhaled or injected

Cell Therapies

Macrophages

-CAR Macrophages can be created to specifically target SARS-CoV-2 antigens
-Macrophage membranes can be used to carry antiviral drug-bearing nanoparticles

Natural Killer Cells

-Can be expanded ex vivo and transfused into patients
-Can be used in combination with conventional or other cell therapies
-Can be armed with CAR constructs to specifically target SARS-CoV-2 antigens

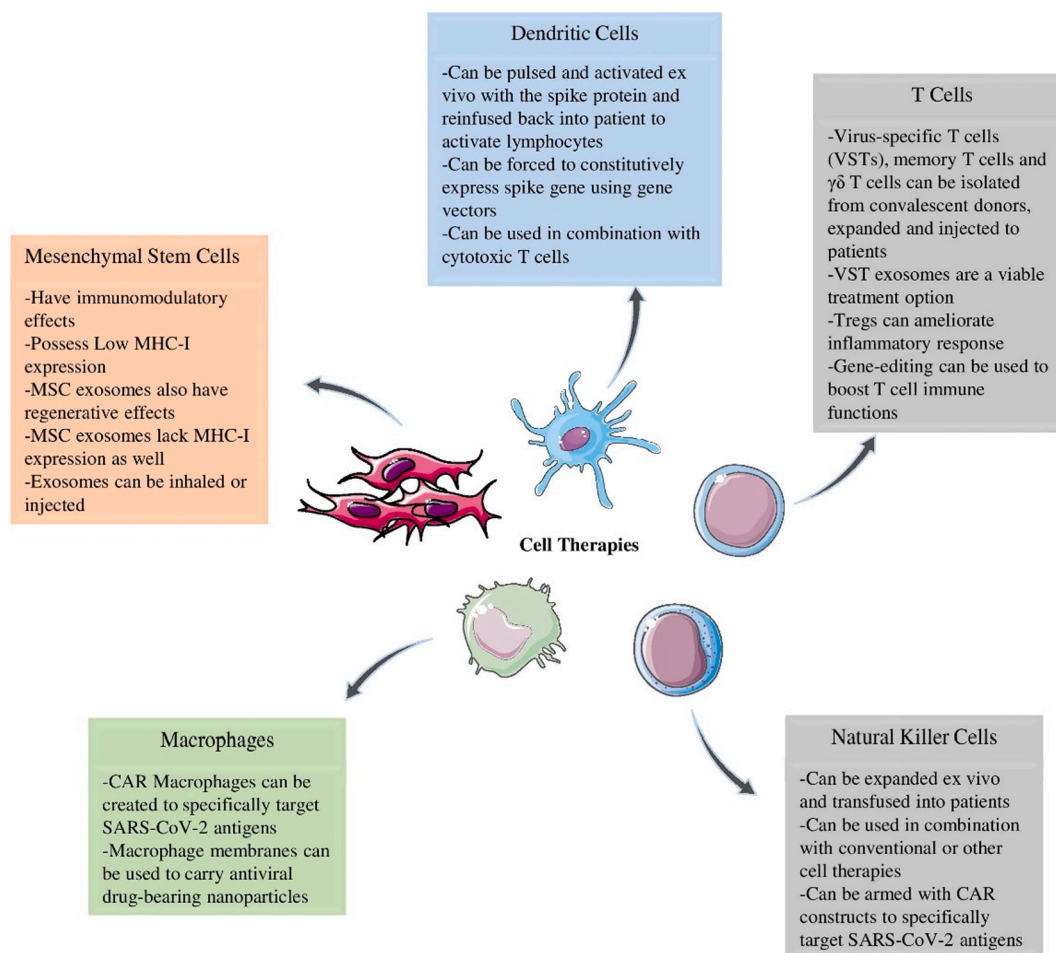**Fig. 2.** The current applications of the most prominent cell-based therapies in COVID-19. (Figure illustrated with the help of https://smart.servier.com/).

(HLA) compatibility. Incompatible HLA of allogenic, unrelated T cells can result in acute or chronic graft-versus-host disease (GVHD), in which the grafted immune cells target the healthy cells of the recipient. CSTC-Exo is one such product. A phase 1 interventional study is investigating the safety and efficacy of these VST-derived exosomes (NCT04389385). CSTC-Exo is administered to early-stage COVID-19 patients via a metered dose inhaler.

The safety and efficacy of different phenotypes of T cells including γδ T cells (NCT04834128) and regulatory T cells (Tregs) (NCT04468971) are being investigated in trials among other unconventional T cell subtypes [45]. γδ T cells constitute a small portion of circulating T cells and exhibit both the innate and adaptive traits of the immune system with a wide antiviral activity independent of the major histocompatibility complex (MHC) molecules [46]. Adoptive transfer of Tregs is beneficial in inflammatory and autoimmune disorders [47] and can be used to dampen the inflammatory response in severe COVID-19 cases. Gladstone *et al.* reported the treatment of ARDS in two patients using *ex vivo* expanded, allogenic HLA-matched, cord blood-derived Tregs, which was associated with diminished IL-6 and TNF-α inflammatory cytokines [48].

3.3. NK cell therapy

NK cells, activated via macrophage-derived cytokines and type I IFNs, are members of the innate immune system which target virus-infected cells. Using a slew of inhibitory (e.g. NKG2A and KIR) and activating (e.g. NKG2D) receptors, NK cells rapidly respond to invading pathogens as they require no MHCs to exert their immune response. Adoptive transfer of NK cells to COVID-19 patients is a viable strategy. These cells can be derived from various stem cells such as induced pluripotent stem cells (iPSCs) (NCT04363346). NKG2A is a common exhaustion marker on both NK cells and CTLs reversely correlated with the number of NK cells and CTLs and their cytokine production. NKG2A is downregulated in recovered patients, making NKG2A inhibition a potential therapy [49].

Chimeric antigen receptors (CARs) are genetically engineered constructs on CAR-T cells designed to specifically recognize and bind to an antigen in order for the T-cell to perform its cytotoxic effect. Initially designed to recognize tumor-associated antigens, CARs can be designed to recognize any antigen. CAR-primed cells are similar to NK cells in that their antigen recognition is independent of MHC molecules, and since NK cells are adept at quelling viral infections, CAR-NK cells are proposed as a potential COVID-19 therapy. A phase I/II trial is aiming to use universal CAR-expressing NK cells that recognize S protein and NKG2DL of infected cells via their ACE2 and NKG2D proteins, respectively (NCT04324996). These NKG2D-ACE2 CAR-NK cells are reportedly engineered to secrete IL-15 superagonist to increase NK cells' survival time after adoptive transfer. These cells also secrete GM-CSF-neutralizing scFv to inhibit CAR-T cell-related neurotoxicity and cytokine release syndrome (CRS). An unpublished *in vitro* study reported the generation of CAR-NK cells armed with scFV of CR3022, a neutralizing antibody for SARS-CoV-2 [50]. Extracellular exosomes of CAR-T cells can also prove to be an effective therapy against SARS-CoV-2. Fu and colleagues have demonstrated that the CAR-T cell-derived exosomes in the CAR-T cell culture media express CAR and contain high concentrations of cytotoxic molecules with no PD-1 expression [51].

3.4. Macrophage therapy

Macrophages can be divided into two subtypes, which are polar opposites of each other. While type 2 (M2) macrophages are designed for an anti-inflammatory response, type 1 (M1) macrophages contribute to inflammation by secreting IL-6 and IL-1β. Any attempt to annul the inflammation caused by M1 or apply M2 macrophage to reduce lung inflammation can be used as a therapeutic approach [52]. One study reported the successful generation of CAR macrophages against SARS-

CoV-2 that reduced the viral load while not increasing the expression of inflammatory cytokines [53]. Other proposed macrophage-related therapies would include the use of anti-CSF1-R and anti-GM-CSF antibodies to inhibit the differentiation of monocytes to macrophages or to inhibit recruitment of macrophages to the lungs by targeting chemokines and their receptors [54]. Recently, Tan *et al.* have developed a drug delivery system that uses macrophage membrane as carriers. PLGA nanoparticles are loaded with lopinavir as antiviral drug and are coated with fragments of macrophage membrane. These mini macrophages release the drug upon contact with SARS-CoV-2 antigen to inactivate the virus. They have also been shown to competitively absorb and neutralize inflammatory cytokines, inhibiting the activation of neutrophils and macrophages [55].

3.5. Mesenchymal stem cell therapy

So far, a large body of studies in the field of cell therapy has been devoted to using stem cells to dampen cytokine storm and ARDS. At the epicenter of these studies, mesenchymal stem/stromal cells (MSCs) have been the main focus [56]. MSCs can be isolated from various sources and are known to have anti-inflammatory and immunomodulatory characteristics [57]; MSCs have been used in the clinic for disorders such as type II diabetes [58] and GVHD [59]. With at least a few dozen clinical trials and scads of preclinical studies, MSCs are suggested to also reduce apoptosis of normal and immune cells, induce an anti-microbial response from innate immunity, prevent damage to alveolar epithelial cells, increase the clearance of alveolar fluids, and reduce multiple organ injuries and ARDS [60]. The immunomodulatory and regenerative effects of MSCs, as well as a lack of ACE2 receptors and their previous success with treating acute lung injury associated with the influenza virus, are the main reasons MSCs are being investigated as a potential treatment for ARDS [61].

A case report of a critically ill patient who was not responding to conventional treatment for 12 days, demonstrated that three times IV administration of allogeneic umbilical cord MSCs (UC-MSCs) improved the overall laboratory indices and symptoms of the patient, and the patient no longer needed mechanical ventilation [62]. In a preliminary study, Leng *et al.* evaluated the therapeutic potential of intravenous (IV) injection of ACE2/TMPRSS2-negative MSCs in 10 patients whose symptoms ranged from moderate to critically ill [63]. Two days after MSC administration, pulmonary functions and clinical symptoms of the patients improved, and reduced CRP and inflammatory cytokines levels were witnessed with no adverse event. In addition, the number of inflammatory cytokine-secreting T and NK cells diminished and, at the same time, total lymphocyte count and regulatory DC population increased. This was discussed to be the effect of MSC anti-inflammatory cytokines. Interestingly, these cells had the capacity to differentiate to type II alveolar epithelial cells [63]. Using the same MSC source, another study conducted a safety experiment in 12 patients who received a single IV dose of UC-MSCs. Starting day 3, clinical symptoms started to dissipate as oxygen saturation and CT results improved significantly. IL-6 concentration, lymphocyte count, and CRP levels were drastically different from the control group by day 7 [64]. Although there were differences of baseline characteristics between groups, and the sample size was small, the favorable results substantiate the efficacy of MSC treatment in COVID-19 patients.

There are currently at least 60 ongoing or completed trials trying to determine the safety and efficacy of MSC therapy for COVID-19, with the majority of trials being in phase 1 or 2 and a few in phase 3 (Table 1). Trials are using a plethora of sources such as dental pulp (NCT04302519), bone marrow (NCT04346368), adipose tissue (NCT04366323), olfactory mucosa (NCT04382547), embryonic stem cells (NCT04331613), and Wharton's jelly (NCT04313322) to extract MSCs. Umbilical cord, bone marrow (BM), and adipose tissue are the most common sources. Allogeneic transplant is more widely used than autologous donation [65]. Autologous sources minimize disease

transmission and immune rejection while allogeneic transplantation is easier and commercially available, yields more cells, and does not expose the patient to biopsy risks. UC-MSCs express the least MHC-1 protein among other sources and do not possess the risk of developing GVHD in allogeneic transplantation [66].

Several trials have focused on evaluating the safety of MSC infusion for ARDS [67–69]. A phase I controlled non-randomized trial investigated the safety of IV transfusion of 3×10^7 UC-MSCs/infusion in three-day intervals in nine COVID-19 patients. Apart from mild fever and facial flushing in two patients and one case of transient hypoxia, no severe adverse effects or mortalities were reported [70]. It was believed that MSCs exert their function by reducing inflammatory cytokines. The patients with various disease severity but high baseline IL-6 levels experienced a significant drop in serum IL-6. In a recent randomized, phase 1/2a, controlled trial, 12 patients with varying levels of ARDS were injected twice with UC-MSCs in three-day intervals (100×10^6 cell/infusion) plus the standard treatment. The treatment proved efficacious as mortality and inflammatory cytokine levels dropped with no significant adverse events [71].

Although MSCs have exhibited potential as a favorable cell therapy approach, there are still some controversies surrounding their safety and scalability [72]. For instance, MSCs can aggregate in blood vessels that might exacerbate the COVID-19-related coagulation disorder and cause further lung dysfunction [18,73]. MSCs release intracellular cytokines and growth factors via extracellular vesicles called exosomes. These secretomes also possess anti-inflammatory, regenerative, and immunomodulatory effects of their parent cells [74], making them a potential therapeutic approach for COVID-19 patients. Exosomes are one of the primary reasons for the immunomodulatory effect of MSCs, and such effects have been demonstrated in cancer, lung injury, *etc.* [75]. They contain a plethora of bioactive molecules and, considering their size, can get past the blood–brain barrier and avert MSC infusion-related pulmonary embolism [76]. Besides the IV injection of secretomes, they can also be administered via inhalation sprays (NCT04276987). Results of clinical studies of exosomes safety and efficacy in COVID-19 patients are scant. In a nonrandomized cohort study, 24 COVID-19 patients received 15 mL of BM-MSC-derived allogeneic exosomes, ExoFlo[TM], and were monitored for 14 days. No adverse effects were witnessed, and 16% of the patients expired due to reasons other than the therapy [77]. In total, 71% of the patients recovered after one injection, and laboratory values and oxygenation improved, indicating the safety and efficacy of MSC exosomes. Still, the results of clinical trials are needed to elucidate the therapeutic potential of MSC exosomes. Some controversies surround the use of exosomes. Although they are more scalable and sustainable than MSCs, a duality exists regarding their tumorigenesis potential. While some studies suggest exosomes can inhibit tumor growth, others believe they can promote tumor metastasis [78]. Secondly, similar to the heterogeneity in MSC populations, MSC exosomes are also heterogeneous. This difference is observed in both the cytokine content [79] and the adverse events of BM-MSC and adipose MSC exosomes [80]. An immortalized MSC cell line can be created to reduce such variations [79].

4. Conclusion and future perspectives

Immune cell-based therapies have shown therapeutic potential in the treatment of malignancies and viral infections. In the context of COVID-19, they can be used to either moderate the hyperinflammatory response of the immune system or bolster it to stave off the disease. Due to various reasons such as high cost and the labor-intensive and time-consuming process associated with generating customized cells, in many disorders, adoptive cell transfer/therapy is not considered the first line of therapy. The existence of corticosteroids in COVID-19 protocols to manage hyperinflammation nullifies immune cell therapies as well.

A lingering issue with any cell-based therapy is the unmatched allogeneic HLA which could result in GVHD in COVID-19 patients. In the case of T cells, VSTs of HLA-typed donors can be expanded ex vivo and cryopreserved for a partially matched allogeneic transplant [39] or HLA-free exosomes derived from such cells can be utilized. The use of HLA-E-restricted CD8+ T cells can also be investigated to circumvent the alloreactivity issue [81]. The secretion of T cell- and MSC-derived exosomes is particularly interesting in this aspect since it requires no previous HLA matching. Gene-editing, which has gained much attention in the past years with the introduction of clustered regularly interspaced short palindromic repeats (CRISPR) and its associated Cas9 protein, may answer this dilemma. CRISPR/Cas9 has shown great results in preclinical and clinical cancer studies to produce CAR-T cells that are directed against a specific tumor antigen, can constitutively secrete stimulatory cytokines, and are less prone to exhaustion [82]. The expression of endogenous TCR and HLA in these cell can also be knocked out to create off-the-shelf CAR-T cells with no risk of GVHD or host-versus-graft reaction [83]. This platform can potentially be used to create universal CAR-T cells or CAR-NK cells that target SARS-CoV-2 antigens with minimal exhaustion by knocking out PD-1/Tim-3 or NKG2A expression.

Despite the ability of infused MSCs to migrate to inflamed sites, their migration rate is relatively low. MSCs depend on certain surface markers, such as, to be chemoattracted from blood to tissue. MSC coating is a promising method to increase cell migration. Cells can be coated with sialyl Lewis X (SLeX), a carbohydrate crucial in the inflammatory extravasation of immune cells [84]. MSCs can also be coated with antibodies against antigens of a target site. MSC coating with anti-vascular cell adhesion molecule 1 (VCAM-1) increases their migration rate compared to regular MSCs and enhances their immunomodulation in inflammatory bowel disease (IBD) [85]. Genetic modification of MSCs has been used to create cytotoxic MSCs that inhibit the growth of tumor cells in preclinical studies [86,87]. MSCs can be engineered to deliver TNF-related apoptosis-inducing ligand (TRAIL) to cancer cells to cause apoptosis [88]. Interestingly, ACE2 can alleviate ARDS, and MSCs that overexpress ACE2 alleviate radiation-related lung injury and ARDS in mouse models [89]. ACE2-overexpressing MSCs exert their anti-inflammatory effects by suppressing ERK1/2 and NF-κB signaling pathways [90]. With the emergence of CRISPR/Cas9 and base editors, this mode of therapy appears to be more feasible [83]. Clinical trials and future studies will have to elucidate the efficacy and safety of cell-based therapies for COVID-19 treatment.

Declaration of Competing Interest

Acknowledgment

Author Contributions

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