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Review article

The immune system as a target for therapy of SARS-CoV-2: A systematic review of the current immunotherapies for COVID-19

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\textbf{ABSTRACT}

\textbf{Aims:} The immune response is essential for the control and resolution of viral infections. Following the outbreak of novel coronavirus disease (COVID-19), several immunotherapies were applied to modulate the immune responses of the affected patients. In this review, we aimed to describe the role of the immune system in response to COVID-19. We also provide a systematic review to collate and describe all published reports of the using immunotherapies, including convalescent plasma therapy, monoclonal antibodies, cytokine therapy, mesenchymal stem cell therapy, and intravenous immunoglobulin and their important outcomes in COVID-19 patients.

\textbf{Material and methods:} A thorough search strategy was applied to identify published research trials in PubMed, Scopus, Medline, and EMBASE from Dec 1, 2019, to May 4, 2020, for studies reporting clinical outcomes of COVID-19 patients treated with immunotherapies along with other standard cares.

\textbf{Key findings:} From an initial screen of 80 identified studies, 24 studies provided clinical outcome data on the use of immunotherapies for the treatment of COVID-19 patients, including convalescent plasma therapy (33 patients), monoclonal antibodies (55 patients), interferon (31 patients), mesenchymal stem cell therapy (8 patient), and immunoglobulin (63 patients). Except for nine severe patients who died after treatment, most patients were recovered from COVID-19 with improved clinical symptoms and laboratory assessment.

\textbf{Significance:} Based on the available evidence, it seems that treatment with immunotherapy along with other standard cares could be an effective and safe approach to modulate the immune system and improvement of clinical outcomes.

1. Introduction

The newly emerged SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), is a positive-sense single-stranded RNA (+ ssRNA) virus that causes COVID-19 (coronavirus disease 2019), which has been getting global concern since December 2019 [1–4]. Coronaviruses belong to the subfamily \textit{Coronavirinae}, in the family \textit{Coronaviridae} of the order \textit{Nidovirales}. Like the other strains of coronavirus, SARS-CoV-2 has phospholipid bilayers envelop and the genome codes almost five types of structural proteins [5–8] (Fig. 1). The typical clinical manifestations of COVID-19 include a non-productive cough, fever, and dyspnea, while acute respiratory distress syndrome (ARDS) is the leading cause of death in COVID-19 [9,10]. Unfortunately, the outbreak is rapidly spreading worldwide. In the absence of effective treatments or vaccines to prevent or treat this infection, its rapid dissemination may affect public healthcare systems and severe economic and social distress worldwide [11,12]. Up to now, several immunotherapy strategies have been used to treat or prevent virus infection in patients with COVID-19 [13]. These approaches, including convalescent plasma therapy, monoclonal antibodies against IL-6 receptor and complement protein C5, cytokine therapy, mesenchymal stem cell therapy, and intravenous immunoglobulin, have been applied with varied efficiency in COVID-19 [14–17]. Interaction of the virus with the immune system mediators leads to triggering an immune response that may determine the outcome of the viral infection [18]. Controlling viral replication in the early phase of the disease could be applied through virus recognition by Pattern recognition receptors (PRRs), including toll-like receptor (TLR), NOD-like receptor (NLR), RIG-I-like receptor (RLR), melanoma

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Fig. 1. Structural proteins of SARS-CoV-2: S protein (spike glycoprotein trimmer), M protein (a type III transmembrane glycoprotein), E protein (located among the S proteins in the virus envelope), N protein (nucleocapsid), HE (hemagglutinin-esterase) dimer (exists in some CoVs).

differentiation-associated gene S (MDA5), C-type lectin-like receptors (CLR), complement proteins, and the other unclassified receptors in the cytoplasm, like Stimulator of interferon genes (STING), DA1, and other innate immune mediators as a part of the innate immune system that may limit SARS-CoV-2 spread within the host [19–23].

According to the recent findings, SARS-CoV-2 replication starts when the S (Spike) proteins attach to the membrane of the lung cells via angiotensin-converting enzyme 2 (ACE2) receptor, by the clathrin-dependent and -independent endocytosis, and release their RNA that senses by endosomal TLRs (TLR3, TLR7, TLR8, and TLR9), RIG-I, MDA5 and cGAS (nucleotidytransferase cyclic GMP-AMP synthase) in the cytoplasm [24–26]. Interactions between SARS-CoV-2 and alveolar cells, trigger downstream signaling pathway via TIR-domain-containing adapter-inducing interferon-β (TRIF), and STING adaptor molecules lead to triggering MyD88 adaptor molecule, following that activation of the NF-κB and interferon regulatory factor 3 (IRF3) [27–29]. The result of this complex pathway is the production of IFN-α and -β and varied set of pro-inflammatory mediators. According to the recently published researches, increased levels of some plasma mediators, including IL-1, IL-2, IL-4, IL-7, IL-10, IL-12, IL-13, IL-17, TNF-α, MIP-1α, IP-10, IFN-γ, GCSF, MCP-1, MCSF, and hepatocyte growth factor (HGF) lead to the lung injury in some patients with COVID-19 [30–33]. The viral invasion occurred, when the virus particles fuse to the respiratory mucosal tissue and infect other cells, resulting in a chain of the immune system responses and cytokine storm, which may be associated with the severe condition of COVID-19 patients [34–36]. In most studies, it was obviously proved that severe pneumonia and consequently respiratory failure and death are due to acute inflammation rather than a direct damaging effect of the virus itself [37,38].

While SARS-CoV-2 attaches and enters the alveolar cells, its antigen will be presented to virus-specific cytotoxic T lymphocytes (CTLs) via major histocompatibility complex (MHC) class I (and less via MHC II) existing on the surface of antigen presentation cells (APC). Antigen presentation subsequently stimulates the cellular and humoral immunity. According to the researches, multiple HLA alleles polymorphisms such as HLA-B*0703, HLA-B*4601, HLA-Cw*0801, HLA-DR B1*1202 have shown a correlation to the susceptibility of SARS-CoV-2 [39,40], while polymorphisms in the HLA-A’0201, HLA-DR30301, and HLA-Cw1502 are related to the protection from SARS infection [41].

According to Wang et al., different subsets of lymphocytes, including CD4+ and CD8+ T lymphocytes, B lymphocytes as well as natural killer (NK) cells are decreased in COVID-19 patients, and this reduction is more significant in the severe cases compared to moderate ones. Peripheral lymphocyte subset alteration is associated with clinical outcome and treatment efficacy of COVID-19 [42]; the number of CD8+ T cells and CD4+/CD8+ ratio showed a significant association with inflammatory status in COVID-19; CD4+/CD8+ ratio was indicated as independent predictors of poor efficacy [41]. While the virus enters the cells, its antigen will be presented to the APC. According to Li et al., the number of TCD4+ and CD8+ in the peripheral blood of COVID-19 patients is significantly reduced. In contrast, they are excessively active, as evidenced by high proportions of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) double-positive fractions [43].

According to the various case studies, those patients who have been infected with SARS-CoV-2 developed a protective antibody, but it is not apparent how long this protection lasts. The quantity and quality of the antibody response may determine the fate of a viral infection [44]. High-affinity neutralizing antibodies can recognize particular viral epitopes without additional mediators via Fc regions. It seems that similar to SARS-CoV infection, in the case of SARS-CoV-2, viral fusing via ACE2 to the lung epithelia is blocked, when neutralizing antibodies recognize the particular domains on the S protein [45,46]. Moreover, these antibodies can also interact with the other immune cells, including NK cells, phagocytes, and complement systems, as a bridge between acquired immune responses and innate immune responses. After recognizing viral antigens via specific antibodies, phosphorylation of ITAMs in the cytoplasmic tail segments of the Iγc and Igβ in B cells occurs by SRC kinase family, lead to trigger downstream signaling to up-regulate pro-inflammatory cytokines and down-regulate anti-inflammatory cytokines [47,48]. Viral components in the endosomes recognized by multiple endosomal TLRs, including TLR3, TLR7, and TLR8, resulting in immunopathology. In this systematic review, we provide an update on the treatment of the COVID-19 patients with focused on the immunotherapies. Immunology knowledge along with
advanced vaccine technology is expected to help us find more effective ways to cure the disease.

2. Methods

This systematic review was conducted based on the Preferred Reporting Items for systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist (Supplementary data, Table 1) [49].

2.1. Search strategy

To identify published research trials in PubMed, Scopus, Medline, and EMBASE from Dec 1, 2019, to May 4, 2020, comprehensive search strategies were performed (Fig. 2). The language was not restricted. We also searched the Clinical Trials.gov, clinicaltrialsregister.eu, and chictr.org for registered ongoing clinical trials. The search keywords are available in Supplementary data, Table 2.

2.2. Study eligibility criteria

Two authors (M.A.H. and S.M.) screened the titles and abstracts from the search results, using the predefined inclusion criteria and excluded duplicate publications. The authors recorded the reasons for excluding studies. Disagreement was resolved through discussion with two more authors (R.N. and M.M.H.R.).

To be eligible, studies had to meet the following criteria:

1) The studies included COVID-19 patients with no restrictions on patient age, sex, and ethnicity.
2) Enrolled patients in the intervention group must have treated with the immunotherapy agents alone or in combination with other drugs, including anti-viral agents, corticosteroids, and antibiotics.

Meanwhile, trials were excluded directly, if:

1) The review articles, systematic reviews, and hypothesis articles.
2) The articles about other respiratory infected diseases such as SARS and MERS.
3) The patients were received other therapies except for immunotherapies, as mentioned above.

2.3. Study quality assessment

Two authors (S.M. and M.M.H.R.) independently evaluated the quality of each publication according to the PRISMA checklist.

2.4. Data extraction

Three authors (M.A.H., S.M., and M.M.H.R.) reviewed the full texts of potentially relevant articles for eligibility according to the inclusion criteria. Then excluded ineligible studies, and documenting reasons for exclusion. The authors extracted data from all included articles to Tables 1 and 2.

3. Results

From an initial screen of 80 identified studies, 24 studies provided clinical outcome data on the use of immunotherapies for the treatment of COVID-19 patients, including convalescent plasma therapy, monoclonal antibodies, interferon, mesenchymal stem cell therapy, and immunoglobulin. Totally, 157 patients met our inclusion criteria that were included in this study. Characteristics of included studies and patient outcomes are summarized in Tables 1 and 2.

3.1. Convalescent plasma therapy

Of 24 studies screened, 6 studies with a total of 33 patients were identified that provided clinical outcomes data on the use of convalescent plasma (CP) therapy for the treatment of COVID-19 patients. These studies include two case reports [50,51], one descriptive study [52], one preliminary uncontrolled case series [53], one pilot study [54], and one retrospective study [55].

Except for one retrospective study that out of 6 patients with COVID-19, only one patient recovered after CP therapy, five studies have shown optimistic results in using CP therapy to treat severe COVID-19 patients.

In one pilot study, one dose of CP collected from recently recovered COVID-19 patients was administered to 10 sever COVID-19 patients. In this trial, the neutralizing antibody titers greater than 1:640 were transfused to the patients in addition to anti-viral drugs and corticosteroid therapy. The outcome was the amelioration of clinical symptoms, pulmonary lesions, pulmonary function, improved lymphocytopenia,
| #  | Author                        | Type of immunotherapy | Treatment by | Number of treated patients | Outcomes                                                                 | Fatality | Ref  |
|----|-------------------------------|-----------------------|--------------|----------------------------|--------------------------------------------------------------------------|----------|------|
| 1  | Ahn JY et al                  | Plasma therapy        | CP           | 2                          | Subsiding the fever, decrease oxygen demand, decreased level of CRP and IL-6 to normal range, chest X-ray improvement, negative SARS-CoV-2 RNA | None     | [50] |
| 2  | Zhang B et al                 | Plasma therapy        | CP           | 4                          | Decreased viral load, increased anti-SARS-CoV-2 titer in serum, chest X-ray improvement | None     | [51] |
| 3  | Mingxiang et al              | Plasma therapy        | CP           | 6                          | Improvement of clinical symptoms, chest X-ray improvement, increased anti-SARS-CoV-2 titer in serum | None     | [52] |
| 4  | Shen C et al                  | Plasma therapy        | CP           | 5                          | Changes of body temperature, improvement Sequential Organ Failure Assessment (SOFA) score, decrease viral load, increased serum antibody titer, decreased CRP level and procalcitoin to the normal range | None     | [53] |
| 5  | Duan K et al                  | Plasma therapy        | CP           | 10                         | Improvement of clinical symptoms, decreased pulmonary lesions, improved pulmonary function, improved lymphocytopenia, decreased SARS-CoV-2 RNA to undetectable level | None     | [54] |
| 6  | Zeng QL et al                 | Plasma therapy        | CP           | 6                          | Decreased viral load, decreased SARS-CoV-2 RNA to undetectable level       | 5 patients | [55] |
| 7  | Xu X et al                    | Monoclonal antibody   | TCZ          | 21                         | Subsiding the fever, decreased level of CRP to normal range (in 16 patients), decreased oxygen demand (in 15 patients), chest X-ray improvement (in 19 patients), little improvement in chest X-ray (in 3 patients) | None     | [57] |
| 8  | Giambenedetto SD et al        | Monoclonal antibody   | TCZ          | 3                          | Subsiding the fever, PaO2/FIO2 ratio improvement, decreased level of CRP to normal range | None     | [58] |
| 9  | Diurno F et al                | Monoclonal antibody   | Eculizumab   | 4                          | Improvement of clinical symptoms and laboratory tests, improvement in chest X-ray | None     | [59] |
| 10 | Fontana F et al               | Monoclonal antibody   | TCZ, IVlg    | 1                          | Subsiding the fever, decreased oxygen demand, Pseudomonas aeruginosa infection in urine culture | None     | [60] |
| 11 | Michot JM                     | Monoclonal antibody   | TCZ          | 1                          | Improvement of clinical symptoms, subsiding the fever, decreased oxygen consumption, chest X-ray improvement, decreased level of CRP to normal range | None     | [61] |
| 12 | Zhang X et al                 | Monoclonal antibody   | TCZ          | 1                          | Disappeared chest tightness, decreased level of IL-6, chest X-ray improvement, decreased the SARS-CoV-2 RNA to undetectable level | None     | [62] |
| 13 | Mihai C et al                 | Monoclonal antibody   | TCZ          | 1                          | Control of arthritis, improvement of musculoskeletal and respiratory symptoms, lung function and chest X-ray improvement | None     | [63] |
| 14 | Morrison AR et al             | Monoclonal antibody   | TCZ          | 2                          | Subsiding the fever, decreased level of inflammatory markers, hypertriglyceridemia, acute pancreatitis (elevated level of lipase and amylase) in one patient with 65 years old age. | None     | [64] |
| 15 | Luna GD et al                 | Monoclonal antibody   | TCZ          | 1                          | Improvement of clinical symptoms | None     | [65] |
| 16 | Cellina Met al                | Monoclonal antibody   | TCZ          | 1                          | Improvement of clinical symptoms and laboratory tests | None     | [66] |
| 17 | Hammami MB et al              | Monoclonal antibody   | TCZ          | 1                          | Subsiding the fever, chest pain and abdominal pain improvement | None     | [67] |
| 18 | Odievre MH et al              | Monoclonal antibody   | TCZ          | 1                          | Improvement of clinical symptoms, decreased oxygen demand, improvement in chest X-ray | None     | [68] |
| 19 | Radbel J et al                | Monoclonal antibody   | TCZ          | 2                          | Worsened the clinical symptoms, myocarditis in one patient, cytopenias, hypertriglyceridemia, elevated ferritin and lactate dehydrogenase, hypofibrinogenemia, decreased level of CRP | 1 patient | [69] |
| 20 | Luo P et al                   | Monoclonal antibody   | TCZ          | 15                         | Death 3/15 Clinical stabilization 9/15 Clinical improvement 1/15 Disease aggravation 2/15 | 3 patients | [70] |
| 21 | Liang B et al                 | Cell therapy          | hUCMSC IVlg  | 1                          | The pneumonia greatly relieved, Improvement of clinical symptoms and laboratory tests, the throat swabs tests reported negative | None     | [71] |
| 22 | Leng Z et al                  | Cell therapy          | MSC          | 7                          | Increased the peripheral lymphocytes, decreased level of CRP | None     | [74] |
| 23 | Xie Y et al                   | Immunoglobulin G      | IVlg, Thymosin | 58                         | Outcomes in treated patients with IVlg within 48 h (<48 h) after admission: reduced the 28-day mortality rate, shorter length of stay in the hospital and/or in ICU, reduced ventilator use. | None     | [75] |
| 24 | Cao W et al                   | Immunoglobulin G      | IVlg          | 3                          | Improvement of clinical symptoms, recovered lymphocyte count, decreased level of ESR and CRP to normal range, chest X-ray improvement | None     | [76] |

CP: convalescent plasma therapy; TCZ: Tocilizumab; hUCMSC: human umbilical cord mesenchymal stem cell.
| N | Gender | Age (y) | Comorbidities | IAI (days) | CPI | TI | Dose/times of transfusion | OT | Ref |
|---|--------|---------|---------------|-----------|-----|----|--------------------------|---|-----|
| 2 | Male   | 71      | None          | 10        | Fever, cough, pneumonia, acute respiratory distress syndrome | CP | Two doses of 250 mL of CP (500 mL in total) at 12 h interval | Lopinavir/ritonavir, methylprednisolone | [50] |
|   | Female | 67      | HTN           | 6         | Fever, myalgia, pneumonia, acute respiratory distress syndrome | CP | Two doses of 250 mL of CP (500 mL in total) at 12 h interval | Lopinavir/ritonavir | |
| 4 | Female | 69      | None          | 17        | Fever                                      | CP | 900 mL of CP in three doses | Arbidol, lopinavir/ritonavir, oseltamivir, IFN-alpha-2b | [51] |
|   | Male   | 55      | COPD          | 11        | Nausea, poor appetite, cough                | CP | 900 mL of CP in three doses | Arbidol, lopinavir/ritonavir, IFN-alpha-2b | |
|   | Male   | 73      | HTN, chronic renal failure | 14       | Cough                                      | CP | 900 mL of CP in three doses | Arbidol, lopinavir/ritonavir, oseltamivir, IFN-alpha-2b, ribavirin | |
| 6 | Male   | 69      | None          | 13        | Fever, myalgia, dyspnea                    | CP | Three doses of 200 mL of CP (600 mL in total) | Arbidol, corticosteroids | [52] |
|   | Female | 75      | None          | 28        | Fatigue, dyspnea                           | CP | Two doses of 200 mL of CP (400 mL in total) | Arbidol, corticosteroids | |
|   | Male   | 56      | Bronchitis    | 31        | Fever, cough                               | CP | Three doses of 200 mL of CP (600 mL in total) | Arbidol, corticosteroids | |
|   | Female | 63      | Sjogren syndrome | 27       | Fever, cough, fatigue, dyspnea             | CP | One dose of 200 mL of CP | Arbidol | |
|   | Female | 28      | None          | 8         | None                                       | CP | One dose of 200 mL of CP | Arbidol, corticosteroids | |
|   | Male   | 57      | None          | 6         | Fever, cough, myalgia, dyspnea             | CP | One dose of 200 mL of CP | Arbidol, corticosteroids | |
| 5 | Male   | 70      | None          | 22        | Bacterial pneumonia; ARDS; multiple organ dysfunction syndrome | CP | Two doses of 200 to 250 mL (400 mL in total) of CP on the same day | Lopinavir/ritonavir, IFN-alpha-1b, favipiravir, methylprednisolone | [53] |
|   | Male   | 60      | HTN, MI       | 10        | Bacterial pneumonia; fungal pneumonia; ARDS; myocardial damage | CP | Two doses of 200 to 250 mL (400 mL in total) of CP on the same day | Lopinavir/ritonavir, arbidol, darunavir, methylprednisolone | |
|   | Female | 50      | None          | 20        | ARDS                                       | CP | Two doses of 200 to 250 mL (400 mL in total) of CP on the same day | Lopinavir/ritonavir, IFN-alpha-1b, methylprednisolone | |
|   | Female | 30      | None          | 19        | ARDS                                       | CP | Two doses of 200 to 250 mL (400 mL in total) of CP on the same day | Lopinavir/ritonavir, IFN-alpha-1b, favipiravir, methylprednisolone | |
|   | Male   | 60      | None          | 20        | ARDS                                       | CP | Two doses of 200 to 250 mL (400 mL in total) of CP on the same day | Lopinavir/ritonavir, IFN-alpha-1b, methylprednisolone | |
| 10 | Male   | 46      | HTN           | 11        | Fever, cough, sputum production, shortness of breath, chest pain | CP | One dose of 200 mL of CP | Arbidol, ribavirin | [54] |
|   | Female | 34      | None          | 11        | Cough, shortness of breath, chest pain, nausea and vomiting | CP | One dose of 200 mL of CP | Arbidol | |
|   | Male   | 42      | HTN           | 19        | Fever, cough, sputum production, shortness of breath, chest pain | CP | One dose of 200 mL of CP | Arbidol, methylprednisolone | |
|   | Female | 55      | None          | 19        | Fever, cough, sputum production, shortness of breath, sore throat, diarrhea | CP | One dose of 200 mL of CP | Ribavirin, methylprednisolone | |
|   | Male   | 57      | None          | 14        | Fever, shortness of breath                  | CP | One dose of 200 mL of CP | Arbidol, remdesivir, IFN-alpha, methylprednisolone | |
|   | Female | 78      | None          | 17        | Fever, cough, sputum production, shortness of breath, muscle ache | CP | One dose of 200 mL of CP | Arbidol, methylprednisolone | |
|   | Male   | 56      | None          | 16        | Fever, cough, sputum production, arthralgia, diarrhea, vomiting | CP | One dose of 200 mL of CP | Arbidol, methylprednisolone | |
|   | Male   | 67      | CD            | 20        | Fever, cough, headache, diarrhea, vomiting | CP | One dose of 200 mL of CP | Arbidol, ribavirin | |
|   | Female | 49      | None          | 10        | Cough, shortness of breath                  | CP | One dose of 200 mL of CP | Arbidol, oseltamivir, Peramivir | |
|   | Male   | 50      | HTN           | 20        | Shortness of breath                         | CP | One dose of 200 mL of CP | Arbidol, IFN-alpha, methylprednisolone | |

(continued on next page)
| N  | Gender | Age (y) | Comorbidities                                                                 | IAI (days) | CPI                                                                 | TI       | Dose/times of transfusion | OT                  | Ref  |
|----|--------|---------|--------------------------------------------------------------------------------|------------|----------------------------------------------------------------------|---------|--------------------------|---------------------|------|
| 6  | Male: 5/6 | Median age: 61.5 | None                                                                          | 4/6        | Median: 21.5 days                                                    | Fever 6/6 | CP | Median volume of CP: 300 ml (200-600) | N/A     | [55] |
|    | Female: 1/6 |         |                                                                                 |            |                                                                     | Cough 6/6 | Fatigue 5/5              |短ness of breath 5/5 | Dyspnea 4/5 |         |        |
| 21 | Male: 18/21 | Range: 56.8 ± 6.5 | HTN                                                                            | 9/21       | Fever 21/21                                                          | TCZ 8 mg/kg IV |            | 18/21 patients received one dose | All patients: Lopinavir, ritonavir, IFN alpha, ribavirin | [57] |
|    | Female: 3/21 |         | Diabetes                                                                        | 5/21       | Cough 14/21                                                          | TCZ       | 3/21 patients received two doses (due to fever within 12 h) | For patients with rapid progress in respiratory function: Methylprednisolone was also administered |        |
|    |         |         | CHD                                                                             | 2/21       | dyspnea 6/21                                                        |           |                          |                     |                  |        |
|    |         |         | COPD                                                                            | 1/21       | Phlegm 9/21                                                          |           |                          |                     |                  |        |
|    |         |         | Brain Infarction                                                                | 1/21       | Fatigue 6/21                                                          |           |                          |                     |                  |        |
|    |         |         |                                                                                 |            | Nausea 4/21                                                          |           |                          |                     |                  |        |
|    |         |         | Stack I, chronic kidney disease stage IIIa, lymphoma, unprovoked pulmonary embolism, urinary tract infection | 11         | Fever 9/11                                                           | TCZ       | Two doses of TCZ at 8 mg/kg IV, 12 h apart | Lopinavir/ritonavir, hydroxychloroquine | [58] |
|    |         |         |                                                                                 |            |                                                                      | IVIg 324 mg of TCZ via subcutaneous route | 0.3 g/kg IVIg | Methylprednisolone, hydroxychloroquine, IVIg | [60] |
| 1  | Male: 71 | HTN     |                                                                                 | 9          | Flu-like symptoms, dyspnea                                           | Eculizumab | Two doses of Eculizumab at 900 mg | Enoxaparin 4000, Lopinavir/ritonavir, hydroxychloroquine | [59] |
|    | Male: 45 | None    |                                                                                 | 4          | Fever, dyspnea, chest pain                                           | TCZ       | Two doses of TCZ at 8 mg/kg IV, 12 h apart | Lopinavir/ritonavir, hydroxychloroquine | [58] |
|    | Male: 53 | HTN     |                                                                                 | 2          | Flu-like symptoms, dyspnea                                           | TCZ       | Three doses of TCZ 12 h after the first and a third dose after further 24-36 h | Lopinavir/ritonavir, hydroxychloroquine | [58] |
| 4  | Female: 54 | β-Thalassemia |                                                                                 | N/A        | Fever, cough, respiratory failure                                    | Eculizumab | Two doses of Eculizumab at 900 mg | Eculizumab | [60] |
|    | Male: 73 | HTN     |                                                                                 | N/A        | Fever, cough, respiratory failure                                    | Eculizumab | Two doses of Eculizumab at 900 mg | Eculizumab | [60] |
|    | Male: 82 | HTN     |                                                                                 | N/A        | Fever, cough, respiratory failure                                    | Eculizumab | Two doses of Eculizumab at 900 mg | Eculizumab | [60] |
|    | Male: 61 | HTN     |                                                                                 | N/A        | Fever, cough, respiratory failure                                    | Eculizumab | Two doses of Eculizumab at 900 mg | Eculizumab | [60] |
| 1  | Male: 42 | MRC     | Kidney transplant, chronic kidney disease stage IIIa, lymphoma, unprovoked pulmonary embolism, urinary tract infection | 11         | Fever 11/11                                                          | TCZ       | Two doses of TCZ at 8 mg/kg IV, 12 h apart | Lopinavir/ritonavir | [61] |
|    | Male: 60 | MM      |                                                                                 | 9          | chest tightness and shortness of breath without fever and cough       | TCZ       | One dose of TCZ at 8 mg/kg IV | Arbidol, methylprednisolone | [62] |
| 1  | Female: 57 | SSC, IDDM, WHO grade I obesity |                                                                                 | N/A        | Cough, dyspnea, arthritis                                             | TCZ       | 8 mg/kg every 4 weeks IV | N/A | [63] |
|    | Male: 65 | None    |                                                                                 | 9          | Fever, ARDS                                                          | TCZ       | Two doses of TCZ | Lopinavir/ritonavir, hydroxychloroquine | [64] |
| 1  | Female: 43 | None    | Respiratory failure, ARDS, fever, fever, pneumonia, acute chest syndrome        | 13         | Fever 13/13                                                          | TCZ       | Two doses of TCZ at 8 mg/kg IV | Hydroychloroquine | [65] |
|    | Male: 45 | SCD     |                                                                                 | 2          | Fever, pneumonia, acute chest syndrome                                | TCZ       | One dose of TCZ at 8 mg/kg IV | Hydroychloroquine | [65] |
| 1  | Male: 65 | None    |                                                                                 | 7          | Syncope, fever, dyspnea                                              | TCZ       | Two doses of TCZ at 8 mg/kg IV, 12 h apart | N/A | [66] |
| 1  | Male: 63 | Liver cancer, liver transplant (end-stage renal disease), HTN, diabetes, peripheral vascular disease, heart failure, smoking | 12         | Fever, cough, fatigue, headache, myalgia, malaise                    | TCZ       | One dose of TCZ at 800 mg (9 mg/kg) | Hydroychloroquine | [67] |
| 1  | Female: 46 | SCD     |                                                                                 | N/A        | Fever, acute chest syndrome, respiratory distress syndrome, fever, septic shock | TCZ       | One dose of TCZ at 8 mg/kg | N/A | Red blood cell exchange transfusion | [68] |
| 2  | Male: 40 | None    |                                                                                 | 4          | Fever, cough, dyspnea, ARDS, septic shock                            | TCZ       | One dose of TCZ at 400 mg | N/A | [69] |
| Female: 69 | Type II diabetes mellitus, rheumatoid arthritis, aplastic anemia | 4 |                                                                                 |            | Fever, cough, chest pain, fatigue, abdominal pain                      | TCZ       | Two dose of TCZ at 560 mg and 700 mg |        |        |

(continued on next page)
| N  | Gender  | Age (y) | Comorbidities | IAI (days) | CPI          | TI            | Dose/times of transfusion | OT                                      | Ref |
|----|---------|---------|---------------|------------|--------------|---------------|--------------------------|-----------------------------------------|-----|
| 15 | Male: 12/15 | 71 ± 9 | HTN + stroke history | 3/15 | 0 | Critically ill | 7/15 | TCZ  | 80–600 mg of TCZ per time. 10/15 patients received one dose of TCZ, 3/15 patients received two dose of TCZ, 2/15 patients received three dose of TCZ | Methylprednisolone: 8/15 None: 2/15 | [70] |
| 15 | Female: 3/15 |         | HTN + diabetes | 2/15 | | Seriously ill | 6/15 | | | |
|     |         |         | Stroke history | 4/15 | | | | | |
|     |         |         |               | 1/15 | | Moderately ill | 2/15 | | | |
| 1  | Female | 65 | N/A | 10 | Fatigue, fever, cough chest tightness | hUCMSC IVig | Three doses of MSC at 5 × 10^7 cells | Lopinavir/ritonavir, IFN-alpha, oseltamivir, methylprednisolone | [71] |
| 7  | Male | 65 | N/A | 8 | Fever, shortness of breath, cough, poor appetite, diarrhea (1/7) | MSC | 1 × 10^6 cells per kilogram of weight | Standard treatments | [74] |
|    | Female | 63 | N/A | 6 | | | | | |
|    | Female | 65 | N/A | 10 | | | | | |
|    | Female | 51 | N/A | 1 | | | | | |
|    | Male | 57 | N/A | 2 | | | | | |
|    | Male | 45 | N/A | 10 | | | | | |
|    | Male | 53 | N/A | 3 | | | | | |
| 58 | Male: 36/22 | Median age: 63 | N/A | > 48 h ≤ 48 h | N/A | IVig | N/A | Arbidol + all other treatment according to WHO (not detected) | [75] |
|    | Female: 58 |         | N/A | | | | | |
| 3  | Male | 56 | None | 7 | Sore throat, fever, cough, dyspnea | IVig | 25 g per day for five days (body weight: 66 kg) | Oseltamivir | [76] |
|    | Male | 34 | HTN | 2 | Fever, cough, dyspnea | IVig | 25 g per day for five days (body weight: 63 kg) | None | |
|    | Female | 35 | None | 6 | Fever, cough, dyspnea | IVig | 25 g/day for five days (body weight: 56 kg) | Lopinavir/ritonavir, corticosteroids | |

Y: years; N: number of patients; IAI: interval between admission and immunotherapy (days); CPI: complication prior to immunotherapy or principal symptoms; TI: type of immunotherapy; OT: other anti-viral and steroid therapies; CP: convalescent plasma therapy; TCZ: Tocilizumab; MSC: mesenchymal stem cell; hUCMSC: human umbilical cord mesenchymal stem cell; ARDS: acute respiratory distress syndrome; HTN: hypertension; MI: mitral insufficiency; CD: cardiovascular and cerebrovascular diseases; MRC: metastatic sarcomatoid clear cell renal cell carcinoma; SSC: systemic sclerosis; IDDM: insulin-dependent type 2 diabetes mellitus; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; MM: multiple myeloma; SCD: homozygous sickle cell disease; N/A: not applicable; CVD: cardiovascular disease.
and decreased the SARS-CoV-2 RNA to an undetectable level [54].

In a case series trial, five COVID-19 patients with severe pneumonia were assessed who were treated with CP therapy. The neutralizing antibody titers above 1:40 were transfused to the patients in addition to anti-viral drugs and corticosteroid therapy. The outcome was an improvement of the clinical symptoms and laboratory assessments including, changes in body temperature, improvement Sequential Organ Failure Assessment (SOFA) score, decrease viral load, increased serum antibody titer, and decreased CRP level to the normal range [53].

One case report study has shown a favorable outcome after CP therapy in two COVID-19 patients with severe pneumonia. Both two cases showed chest X-ray improvement, decrease oxygen demand, and subsiding the fever. Their laboratory assessments showed a reduced level of CRP and IL-6 to the normal range and negative SARS-COV-2 RNA [50].

In a descriptive study by Mingxiang et al., six COVID-19 patients were treated with CP therapy. An increased titer of anti-SARS-COV-2 and computed tomography (CT) scan improvement were observed in all six patients [52].

Zhang B et al. evaluated the efficiency of CP therapy in 4 patients. The viral load significantly dropped in one case after CP transfusion. Totally, decreased viral load was observed in 3–22 days and anti-SARS-COV-2 IgG was developed in all patients in this trial 14 days after CP therapy [51]. On the other hand, researchers at Johns Hopkins University obtained FDA approval to test CP therapy for COVID19 patients in large-scale clinical trials [56]. By 4th May 2020, there were 11 clinical trials registered in China (Supplementary data, Table 3) and 43 trials have registered in clinicaltrials.gov (Supplementary data, Table 4) for large-scale treatment of COVID-19 patients with CP.

3.2. Monoclonal antibodies

Of the 24 included studies screened, 14 studies with a total of 55 patients have identified that met inclusion criteria for monoclonal antibodies, including 3 case series [57–59], 10 case reports [60–69], and one retrospective study [70].

Except for four patients who were successfully treated with Eculizumab [59], the others (51 patients) were treated with Tocilizumab (TCZ). One patient also received intravenous immunoglobulin (IVIg) in combination with TCZ [60]. 47 patients were recovered after TCZ; among them, 4 patients have shown adverse effects [60,64,69]. The fatality was also reported in 4 patients, who received TCZ [69,70].

In a case series study, 21 severe COVID-19 patients were treated with TCZ. Improvement of clinical symptoms in this trial was observed within a few days. Fifteen of the 20 patients had reduced demand for oxygen, and one patient did not require oxygen therapy within five days after TCZ. In 16 of the 19 patients, the elevated C-reactive protein (CRP) levels returned to normal range. Improvement in Chest X-rays was observed in 19 cases, and other patients showed little improvement in their chest X-rays [59]. In accordance with this trial, 3 studies have also shown improved clinical symptoms and laboratory tests after TCZ treatment [58,65,66].

Three studies have assessed the TCZ effectiveness in treating patients with cancer or autoimmune disorders. In the first study, treatment with TCZ with favorable outcome was reported in a patient with metastatic sarcomatoid clear cell renal cell carcinoma, including gradually decreased oxygen consumption, improvement in chest CT, and decreased level of CRP. However, it should be noted that this patient had an immunosuppressed condition due to his cancer [61]. The second study reported a patient with multiple myeloma (MM) who was successfully treated with TCZ. The outcomes in this trial were improved in chest tightness and chest CT, decreased level of IL-6, and decreased the SARS-CoV-2 RNA to undetectable levels [62]. Another study demonstrated TCZ performance in a patient with systemic sclerosis and IDDM. Treatment with TCZ in this trial improved musculoskeletal and respiratory symptoms, lung function, and CT imaging [63].

Two studies evaluated the efficacy of TCZ in two patients with organ transplantation [60,67]. Subsiding the fever, decreased oxygen demand, and Pseudomonas aeruginosa infection in urine culture were seen in one of them who was treated with TCZ and IVIg [60]. Another patient showed the reduced fever, improved chest pain and abdominal pain [67].

The adverse effects of TCZ were reported in three studies. Two studies have shown hypertriglycerideremia in four COVID-19 patients treated with TCZ. Hypertriglycerideremia could be related to the disruption of triglyceride uptake which caused by TCZ. Besides, cytopenias, hypertriglycerideremia, elevated ferritin and lactate dehydrogenase, hypofibrinogenemia [69] and acute pancreatitis (elevated level of lipase and amylase) [64] have been also shown in two studies. In another study [60], in a patient with chronic kidney disease stage IIIa, Pseudomonas aeruginosa infection was found in the urinary culture as an adverse effect of TCZ.

One study [70] reported disease aggravation after treatment with TCZ in COVID-19 patients. In this trial, among 15 patients who were treated with TCZ, two patients showed disease aggravation, nine patients showed clinical stabilization, one patient showed clinical improvement, and three patients died.

One study reported treatment with TCZ in COVID-19 pediatric patients with homozygous sickle cell disease (SCD) who was treated successfully [68].

A total number of 29 clinical trials were registered in clinicaltrials.gov until 4 May 2020 in order to evaluate the efficacy of TCZ for treatment of COVID-19 patients (Supplementary data, Table 5). Moreover, some of the clinical trials have been approved for the efficacy assessment of other monoclonal antibodies, including Adalimumab, Camrelizumab, Eculizumab, Meplazumab, PD-1 mab, Anakinra, and Siltuximab to treatment of COVID-19 patients. These monoclonal antibodies are summarized in Supplementary data, Table 6.

3.3. Cytokines and interferons

Of the 24 studies included, 5 studies [51,53,54,57,71] with a total of 31 patients included that received type 1 interferon (IFN) apart from other immunotherapies. These studies include one case report [51], one preliminary uncontrolled case series [53], one pilot study [54], one retrospective study [57], and one case report in registered clinical trials in china [71].

Three patients received IFN-α-2b apart from CP therapy and anti-viral drugs. Among them, two patients had comorbidities including chronic obstructive pulmonary disease (COPD) and chronic renal failure. In this trial, decreased viral load, increased anti-SARS-COV-2 titer in serum, and improvement in chest X-rays were observed in all three patients [51].

Four patients received IFN-α-1b apart from CP therapy, anti-viral drugs, and methylprednisolone. The outcome was including changes in body temperature, improved Sequential Organ Failure Assessment (SOFA) score, decreased viral load, increased serum antibody titer, decreased CRP and procalcitonin levels to the normal range [53].

Type of IFN-α has not mentioned in 24 other patients [54,57,71]. Among them, two patients received IFN-α apart from CP therapy, anti-viral drugs, and methylprednisolone. Amelioration of clinical symptoms, decreased pulmonary lesions, improved pulmonary function, improved lymphocytopenia, and decreased the SARS-CoV-2 RNA to an undetectable level were observed upon treatment [54].

21 patients received IFN-α apart from Tocilizumab, anti-viral drugs, with or without methylprednisolone [57].

One patient received IFN-α apart from human umbilical cord mesenchymal stem cell (huCMSC), IVIg, anti-viral drugs, and methylprednisolone. The outcome was an improvement of clinical symptoms and laboratory tests [71].

Treatment with IFN-α in combination with anti-viral drugs such as ribavirin is recommended for treatment COVID-19 patients in china
There are also 20 registered clinical trials up to 4 May 2020 to evaluate the treatment efficiency of COVID-19 patients with IFN in clinicaltrials.gov (Supplementary data, Table 7). Besides, there were two ongoing clinical trials in China for evaluating the efficacy of recombinant human interleukin-2 [ChiCTR2000030167] and G-CSF [ChiCTR2000030007] in combination with standard treatment in COVID-19 patients.

3.4. Mesenchymal stem cell therapy (MSC)

Out of the 24 studies included, two studies, with a total of 8 patients included a case-control study with 7 patients in the treatment group and 3 in the control group [74], a case report in registered China clinical trials [71] were identified that received MSC.

In the first case study carried out in China, a 65 years old woman with severe pneumonia was treated with the umbilical cord stem cells, apart from IVIg, IFN-α, anti-viral drugs, and methylprednisolone [71]. Before stem cell therapy, the patient had respiratory and multi-organ failure requiring mechanical ventilation. She was not responding to conventional therapy. So, she received three doses of allogeneic stem cells (50 million per dose) within three days, along with conventional therapy. One day after the second infusion, her vital signs were stabilized and she was no longer requiring the ventilator. Two days upon the third dose, she was getting out of the ICU and most of the laboratory indexes were normal. Two days upon the third dose, her throat specimen was negative for Coronavirus. Finally, six days after the third infusion, the CT scan of her lungs significantly improved.

Another study was a short-term (14 days follow-up) and a small clinical trial with only 10 coronavirus patients [74]. The patients were divided into 7 patients (including 1 critically serious, 4 serious, and 2 commons) who were treated with one dose of stem cells and 3 serious patients in the control group who did not. The patients were not responding to standard conventional therapy. All 7 patients were recovered following the receiving stem cell therapy. Conversely, the results obtained from the control group were one dead, one patient with AKI, one patient with sepsis, and one patient with multi-organ failure requiring mechanical ventilation. She was not responding to conventional therapy. One day after the second infusion, she was getting out of the ICU and most of the laboratory indexes were normal. Two days upon the third dose, her throat specimen was negative for Coronavirus. Finally, six days after the third infusion, the CT scan of her lungs significantly improved.

There are also 29 registered clinical trials up to 4 May, to evaluate the treatment efficiency of COVID-19 patients by cell therapy including MSC in clinicaltrials.gov (Supplementary data, Table 8).

3.5. Intravenous immunoglobulin (IVIg)

Of the 24 studies included, 4 observational studies with a total of 63 patients were identified that received IVIg apart from anti viral drugs or other immunotherapies. These studies included one case report [60], one case report in registered china clinical trials [71], one retrospective study [75], and one case series [76].

Among them, one patient received IVIg alone [76], 60 patients received IVIg apart from anti-viral drugs or corticosteroids [75,76], one patient received IVIg apart from Tocilizumab, corticosteroid, and hydroxychloroquine [60], and one patient received IVIg apart from hUCMSC, IFN-alpha, anti viral, and corticosteroid [71].

In the first clinical trial, three patients were treated with anti-viral drugs and IVIg (0.3–0.5 g per kg weight per day for five days) in about one week after admission (in two patients) and 2 days after admission (in one patient). The clinical observations in all three patients were improved, including fever, CT-scan, and oxygen consumption [76].

In the second study, 28-day mortality rate was assessed in 58 severe COVID-19 patients who were treated with IVIg in China. The patients were divided into two groups, the patients who received IVIg within 48 h (<48 h) after admission and the patients who received IVIg > 48 h after admission. All patients received IVIg when their total lymphocyte count decreased to < 0.5 × 10^9/L at 20 g/day. The patients were also treated with Thymosin if the total number of lymphocytes had not increased 5 days after IVIg administration. The results showed the reduced 28-day mortality rate, reduced ventilator use, and shorter length of stay in hospital in the patients who received IVIg within 48 h after admission in comparison to the patients who received IVIg > 48 h after admission [75].

One study assessed the efficiency of IVIg in a COVID-19 patient with chronic kidney disease stage IIIa. In this trial, the patient received IVIg at the dose of 0.3 g/kg, Tocilizumab, hydroxychloroquine, corticosteroid, and cyclosporine A. The outcome was a subsiding the fever and normal peripheral oxygen saturation. Progressive leukopenia and neutropenia, stopped oxygen treatment, and stability in kidney function were observed after Tocilizumab, and then IVIg was administered to immune system modulation [60].

3.6. Other registered clinical trials

In addition to the mentioned ongoing clinical trials, we found five clinical trials for Thymosin (Supplementary data, Table 9) and four clinical trials for immunosuppressive drugs, including Fingolimod, Leflunomide, Thalidomide (Supplementary data, Table 10) in order to evaluate their efficiency in COVID-19 patients.

4. Discussion

SARS-CoV-2 is a newly emerged pathogen that spreads quickly and could result in acute respiratory distress syndrome in infected patients. SARS-CoV-2 and SARS-CoV share about 79% genomic similarity, caused to bind to the same receptor (ACE2R) that found in the lung epithelium and some other tissues. No efficient drug is available for treatment at the moment [48,77]. Meanwhile, the immune system is facing many challenges and there is still a lot of uncertainty about the immune responses in this disease as well as the role of the individual components of the immune system, the effect of antibody responses, duration of immunity, the most effective treatment, and so on. So the efficacy of the innate, cellular, and humoral immunity determines the outcome of viral infections. It means a proper immune response mediates protection, while an overwhelming immune response is associated with immune-mediated pathogenesis in viral infections. Many efforts are currently being made to find effective treatment worldwide, and each has shown different outcomes. Since a lot of different immunotherapies are in processing, we hope that we could see the elimination of this virus via immunotherapy like the other previous viral pandemics (Fig. 3).

Convalescent plasma therapy is referred to use plasma containing antibodies from a person who has recovered from an illness. Accumulating evidence suggests the effective role of CP therapy in various viral respiratory disorders. The hopeful outcomes of CP therapy, including improved survival rate and reduced mortality of the patients have been reported in SARS-CoV related pneumonia and influenza A (H1N1) [78–82].

It seems that CP therapy could be used in newly infected COVID-19 patients to improve the immune response, probably through neutralizing the virus, suppress viremia, and viral clearance. No adverse effects were observed in all included patients in this study. Nevertheless, some precautions should be considered, including evaluating the neutralizing Ab activity titer and accurate time for plasma collection and administration [83]. Besides, CP therapy might be more effective if administered at the initial stage of the disease [55,79].

Immunotherapy using monoclonal antibodies as another inspiring approach is progressing to treat COVID-19 patients [84]. Up to now, most clinical trials have been performed on TCZ. However, one study reported good results in treating patients with Eculizumab, a
humanized monoclonal antibody against complement protein C5.

TCZ is a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that has long been used to treat various inflammatory disorders including rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, Castleman disease, and Crohn’s disease. The effective use of TCZ is also reported in the treatment of cytokine release syndrome (CRS) that has occurred in various conditions such as CAR-T cell therapy, organ transplantation, and virus infection [85–90].

The high level of serum cytokines, including IL-6, IL-1, IL-8, IL-12, and tumor necrosis factor-alpha (TNF-α) is reported to be associated with the severe acute respiratory syndrome (SARS) in coronavirus infection [33,91–93]. It has been described that the COVID-19 patients had a high level of cytokines and chemokines in serum including IL-6, IL-2, TNF-α, IL-10, interferon-gamma inducible protein (IP-10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein (MIP1α) that was related to an inflammatory condition in the patients known as cytokine storm that is associated with the severity of the disease [94]. TCZ can modulate immune responses through the interaction with soluble or membrane-bound IL-6R and subsequently inhibits IL-6 signaling [95]. Interestingly, anti-virus immune response by plasma B cells and CD8+ T cells were seen in the treated patients with TCZ suggesting the specific effect of TCZ on inflammatory cascade [96].

Treatment with TCZ in COVID-19 patients who have elevated levels of inflammatory cytokine IL-6 might be effective in modulating inflammatory response caused by cytokines storm.

Although treatment with TCZ had inspiring outcomes, some adverse effects were also reported such as hypertriglyceridemia in four patients and Pseudomonas aeruginosa infection in urine culture in one patient with chronic kidney disease [60,64,69]. Besides, two patients have shown disease aggravation after treatment with TCZ [70]. As a result, more investigations in large scale trials are needed for evaluating the efficacy of TCZ in COVID-19 patients.

Two in-vitro studies by Wang et al., and Tian et al., also revealed two types of monoclonal antibodies named 47D11 [97] and CR3022 [98] with the neutralizing effect of SARS-COV-2. These studies could be helpful to improve our knowledge to design effective monoclonal antibodies to treat COVID-19 patients.

Cytokine therapy is also another approach to treat COVID-19 patients. Type 1 interferons (IFN-1) are a group of cytokines produced by various types of immune cells, particularly plasmacytoid dendritic cells during the first stages of a response against viral infection [99]. Different subtypes of IFN-1 are recognized including α, β, ϵ, ω, and κ [100].

It has been shown that IFN-1 could be an efficient agent against
various viral infections including hepatitis B, C, and HIV [101]. An in vitro study showed that SARS-CoV-2 is more sensitive to IFN-I compared to SARS-CoV. This discrepancy may be due to the changes that occurred in proteins of SARS-CoV-2, such as the loss of ORF3b, that would be resulted in a changed response to IFN-I [102]. After treatment COVID-19 patients with IFN-I along with other standard cares, favorable outcomes were observed due to improvement of the anti-viral response.

IVIG is referred to as polyclonal IgG isolated from healthy donors. IVlg has long been used to treat the patients, who suffered from primary antibody deficiencies, vasculitis, rheumatologic disorders, chronic inflammatory diseases, systemic lupus erythematosus (SLE) as well as treat several hematological and neurological disorders [103]. Treatment with IVlg has also been effective in the treatment or prevention of the infectious disease caused by viruses, bacteria, and fungi in human patients [104,105].

Previous studies were shown the encouraging outcomes in patients with SARS and MERS after treatment with IVlg [106–108]. Using IVlg for COVID-19 treatment has been performed only in a small number of patients. Good results were observed after treatment with IVlg in combination with other standard anti-viral drugs. The immune system modulation by IVlg could be conducted by improving passive immunity and anti-inflammatory response. Although the role of IVlg in COVID-19 patients requires more investigations, it seems that this approach has promising effects, if administered in the early stage of disease.

Cell-based therapies have been used to management of several illnesses including pulmonary [109–111], cardiovascular [112,113], hepatic [114], and renal [115] diseases. Also, the safety and effectiveness of the treatment with stem cells have been documented in many clinical trials, especially in immune-mediated inflammatory diseases, such as SLE and graft-versus-host disease (GVHD) [110,116].

In line with finding effective drug therapies and immunological treatments for COVID-19, mesenchymal stem cells (MSCs) may have significant immunomodulatory ability. On the other hand, these cells secrete many anti-inflammatory factors through paracrine route or direct interactions with immune cells, including T and B cells, macrophages, dendritic cells (DCs), and NK cells. The outcome of these events may lead to preventing or inhibiting the cytokine storm, regulating the inflammatory response as well as decreased morbidity and mortality in the treated patients.

Until now, many worldwide health centers have released several guidelines related to treating coronavirus patients using MSCs. For example, the Italian College of Anesthesia, Analgesia, Resuscitation, and Intensive Care has stated that stem cells have a significant potential to treat COVID-19 patients by decreasing the need to ICU care. Based on FDA regulations, stem cell therapy is commonly used to treat various morbidity conditions. In this way, some clinical trials (mainly performed in China) have shown the safety and efficacy of this type of therapy method [116–118]. The reported findings from these clinical trials showed that stem cell therapy likely is ideal to treat coronavirus as a serious systemic illness. The primary sources of stem cells available for this purpose are autologous bone marrow stem cells [116], adipose stem cells, amniotic stem cells, and umbilical cord stem cells. Among them, the umbilical cord as a promising source of MSCs, due to transplantation across MHC barriers seems to be the most desirable source to treat coronavirus [69,71,112].

Two potential mechanisms have been proposed by which MSCs can treat COVID-19 patients, including the immune system modulation and also promote tissue repair and regeneration. The most complications induced by the coronavirus in the vital organs occurred in the lungs. Studies have reported that upon intravenous infusion, the majority of the MSCs accumulate in the lung, which could potentially result in the improvement of the pulmonary microenvironment of the alveolar epithelial cells and also inhibition of pulmonary fibrosis.

Besides, several studies reported that MSCs also show the anti-microbial effects during infection and inflammation that occurred in preclinical models of sepsis, ARDS, and cystic fibrosis infection. The mechanism of action proposed for their antimicrobial activities are the dynamic coordination of the pro- and anti-inflammatory elements of the immune system or increasing the activity of phagocytes, and also the secretion of antimicrobial factors and molecules [119,120]. In conclusion, umbilical cord MSCs as a main type of the stem cells show a gene expression profile more similar to that of embryonic stem cells due to the fact that they have faster doubling times, more plasticity, and possibly more potency. Fortunately, unlike embryonic stem cells, they are not tumorigenic [121]. Thus, MSCs therapy against COVID-19 could be a promising approach to managing this world-threatening disease. However, the appropriate cell dose, cell concentration, the cell infusion rate should be determined to maximize efficacy and safety. Cell passage numbers should be limited to increase potency and decrease cell size.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

Author contributions

R.N. directed the project. M.A.H., S.M., and R.N. designed research. Data extraction performed by M.A.H., S.M., and M.M.H.R. The paper was drafted by M.A.H., S.M., and M.M.H.R. R.N. did critical revision of the paper. All the authors contributed to protocol development, read and finally approved the paper.

Appendix A. Supplementary data

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