EXPERT OPINION ON BIOLOGICAL THERAPY
2020, VOL. 20, NO. 10, 1111–1115
https://doi.org/10.1080/14712598.2020.1807933

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EDITORIAL

Immunotherapy for SARS-CoV-2: potential opportunities

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ARTICLE HISTORY Received 21 May 2020; Accepted 6 August 2020

KEYWORDS Immunotherapy; monoclonal antibodies; severe acute respiratory syndrome coronavirus 2; COVID-19

1. Introduction

Coronavirus Disease 2019 (COVID-19), caused by a novel coronavirus, called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), emerged at the end of 2019 in Wuhan, Hubei province of China has affected almost all countries worldwide [1,2]. World Health Organization (WHO) expressed the COVID-19 pandemic as a public health emergency of international concern on 30 January 2020 [3].

SARS-CoV-2 is containing a large (approximately 27–32kb nucleotides) single-stranded positive-sense RNA genome, which encodes the eight non-structural proteins and also the 4 structural proteins, such as Membrane (M), Nucleocapsid (N), Envelope (E), and Spike (S) proteins [4,5].

There has been neither approved effective vaccine nor specific antiviral agents against SARS-CoV-2 until now. The most effective treatment option to fight SARS-CoV-2 can be based on the use of specific therapeutic biological agents such as neutralizing monoclonal antibodies and virus entry inhibitors, which interfere in each step of the viral lifecycle [6]. Experiences in fighting other beta-coronaviruses members, such as SARS-CoV and MERS-CoV, have been proposed immunotherapy as an attractive option to fight SARS-CoV-2 [7–9]. In this paper, an overview of the immunotherapy strategies for COVID-19 is presented.

2. Immunotherapies against SARS-CoV-2 virus

2.1. Human monoclonal antibody

Infections with SARS-CoV and SARS-CoV-2 are begun with the virus entry to the host cells through interaction of the receptor-binding domain (RBD) of the S1 subunit in viral spike (S) proteins on the surface of the virus with angiotensin-converting enzyme 2 (ACE2) on host cells [10]. Therefore, spike protein plays a key role in virus entry and the beginning of the viral lifecycle. Accordingly, interruption in the interaction of these proteins with specific neutralizing monoclonal antibodies can be a potential target for effective treatment against coronavirus infections. The neutralizing monoclonal antibodies either against ACE2 or receptor-binding domain (RBD) for SARS-CoV treatment can be helpful for SARS-CoV-2 [11]. With this in mind, Sui *et al*. in an *in vitro* study had reported 80 R scFv (single-chain variable fragment) is a human recombinant monoclonal antibody that binds to S1 domain of S protein of SARS-CoV and prevents the interaction of the virus with host cells that was tested by microneutralization assay and in another study by Sui *et al*. had shown intraperitoneal (IP) of 80 R IgG1 injected to BALB/c mice 1 day before SARS-CoV intranasal challenge, and 80 R IgG1 inhibited the replication of SARS-CoV in lung tissue of mice and its And its prophylactic role was highlighted [12,13].

Moreover, another *in vitro* and *in vivo* animal (Ferret) studies indicated CR3014 is a human IgG1 mAb against recombinant S1 subunit (residues 318–510 that residue N479 was most important for binding to CR3014) and inhibits entrance of SARS-CoV to host cells [11,14]. Besides, Mulen J *et al*. reported the SARS-CoV can be neutralized via binding of CR3022 human IgG1 mAb to recombinant S1 fragment (amino acid residues 318–510) by *in vitro* study. Therefore, These mAbs inhibit the interaction of RBD with cellular receptor ACE2 through binding to the S1 subunit in SARS-CoV which indicated promising findings *in vitro* and *in vivo* studies which are probably going to be effective against SARS-CoV-2 [11,15]. What's more, Wang *et al*. identified the human 47D11 IgG1 monoclonal antibody that binds to full-length spike protein of SARS-CoV and SARS-CoV-2 by an *in vitro* study. 47D11 neutralizes SARS-CoV-2 via blocking virus entry to host cells and protects of uninfected host cells as well as this mAb is useful for development serological assays for the detection of antigens which is related to SARS-CoV-2 [16].

CD147 (also known as Basigin or EMMPRIN) is a type I transmembrane glycoprotein and is described as a novel cellular receptor on host cells for SARS-CoV-2. Meplazumab is an anti-CD147 which is a humanized IgG2 monoclonal antibody and inhibited SARS-CoV-2 entry to host cells. In phase II clinical trial (ClinicalTrials.gov Identifier: NCT04275245) study, it has been investigated the safety and efficacy of infusion of 10 mg Meplazumab intravenously (every day for 2 days) in 17 enrolled patients with COVID-19 after disease onset. Monitoring virion clearance rate at day 3, day 7, and day 14 by Real-time PCR showed as a primary outcome. Secondary outcomes consisted of reduced C-reactive protein (CRP) level,

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lymphocyte count returned to normal, Oxygen saturation (SpO_2) recovered to baseline, significantly improved clinical outcomes, and also hospitalization time reduced in severe SARS-CoV-2 pneumonia cases. No adverse effect was observed in patients treated by meplazumab [17].

2.2. Anti-inflammatory therapies

Following entry of SARS-CoV-2 into the cells through ACE-2 which is overexpressed in special cells such as lung epithelial cells, especially type II pneumocytes, can activate innate and adaptive immune responses. Infected cells with SARS-CoV-2 release Interleukine-8 (IL-8) to infiltration of alveolar macrophages and mononuclear inflammatory cells to infected tissues, and then T and B lymphocytes responses are triggered. To that end, several signaling pathways play a key role to enhance inflammatory responses, such as Janus kinase transducers (JAK/STAT) that is led macrophage activation syndrome (MAS) and increased secretion of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-7, IL-10, granulocyte-colony-stimulating factor (G-CSF), interferon-γ-inducible protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1 alpha (MIP1A) and tumor necrosis factor α (TNF-α). In COVID-19 patients, elevated levels of pro-inflammatory cytokines are associated with immune cell recruitment and then exaggerated inflammation, type II pneumocyte hyperplasia, hyaline membrane formation, and disease progression [18,19].

Therefore, following lung tissue damage, increased secretion of inflammatory cytokines is seen in a majority of the COVID-19 patients. Elevated serum levels of IL-1, IL-6, TNF-α, IFN-ɣ, and CRP are detected in cytokine release syndrome (CRS) in patients with severe COVID-19 which in turn will cause acute respiratory distress syndrome (ARDS) and multiple organ failure, the final result being death. Thus, targeting various players of inflammation via different immunotherapies is currently being evaluated.

IL-1β is an important cytokine released during pyroptosis and acts through autocrine stimulation of tissue macrophages leading to further inflammatory cytokines production [20]. Recombinant IL-1 receptor antagonist (rIL-1Ra, Anakinra) blocks the binding of both IL-1α and IL-1β to the IL-1 receptor, thereupon inhibits IL-1 pro-inflammatory effects. In an ongoing phase III randomized controlled trial study, anakinra has been used in septic patients with MAS and can prevent cytokine storm, and also this caused a significant survival rate without obvious adverse effects [18]. In a phase III trial (ClinicalTrials.gov Identifiers: NCT04330638) is under evaluation of the treatment of COVID-19 patients (n = 342) with combinational of anti–interleukin monoclonal antibodies including daily subcutaneous injections of 100 mg anakinra for 28 days to prevents cytokine release syndrome and onset of ARDS [21].

Pathogenic IFN-ɣ$^+$ GM-CSF$^+$ TH1 cells secrete GM-CSF to promote inflammatory CD14$^+$CD16$^+$ monocyte responses with an increase of IL-6 level in COVID-19 patients [19]. Another inflammatory agent which can be a good target for the treatment of severe cases of COVID-19 is IFN-ɣ. Emapalumab, is an anti-IFN-ɣ monoclonal antibody that FDA approved for primary hemophagocytic lymphohistiocytosis (HLH) and may be effective in MAS. Emapalumab is under investigation in a phase II trial study (ClinicalTrials.gov Identifiers: NCT04324021), to evaluate the safety and efficacy of intravenous infusion every third day in severe COVID-19 patients [21]. Also, granulocyte–macrophage colony-stimulating factor (GM-CSF) is an attractive target as a therapeutic target in COVID-19. TJ003234 is an anti-GM-CSF monoclonal antibody and may be inhibited the infiltration of granulocytes and monocytes. The safety and efficacy of TJ003234 intravenous injection is currently being tested in a randomized, multicenter, double-blind, placebo-controlled, phase Ib/II trial study (ClinicalTrials.gov Identifiers: NCT04341116) in 144 patients with severe COVID-19 [21,22].

The first reports from China showed a high level of plasma concentration of IL-6 in COVID-19 patients. Thus, the context was prepared for the introduction of anti-IL-6 therapies in clinical trials. IL-6 responses induced by SARS N protein and may mediate SARS-CoV-2 lung pathology. Also, IL-6 has been indicated to have an important role in TH17 differentiation by STAT3 activation through JAK1/JAK2 signaling. TH17 cells in turn stimulates the secretion of IL-1, IL-6, IL-8, MCP-1, and TNF-α and GM-CSF, which are associated with inflammation-associated lung damage in SARS-CoV-2 infection [23].

Inhibition of either IL-6 (Siltuximab, chimeric monoclonal antibody) or IL-6 receptor (Tocilizumab, humanized monoclonal antibody) are under investigation in COVID-19 patients [24].

Also, small molecules against other inflammatory agents such as Janus kinase (JAK1/JAK2) inhibitors such as baricitinib (JAK1/JAK2 inhibitor) and fedratinib (JAK2 inhibitor), is under evaluating in COVID-19 patients in randomized clinical trials and may be appropriate for SARS-CoV-2 treatments through impairing in TH17 cells differentiation, also decrease type-I-IFN-mediated antiviral responses and cause alleviating inflammation [21,23].

2.3. Passive immunotherapy

2.3.1. Convalescent plasma therapy

At first Passive antibody therapy was developed in the 1890s and used for treating several infectious diseases until in the 1940s the antimicrobial therapy was generated. Convalescent plasma treatment is passive polyclonal antibody administration to supply immunity against viral infections and improves survival rate, which is called passive immunotherapy. Convalescent plasma therapy may provide an immunomodulatory effect via inhibition of macrophage activation and cytokine storm. Studies on sera of patients treated with COVID-19 have shown the presence of seropositive antibodies against SARS-CoV-2 in serum such as IgG, IgM, and IgA with varying sensitivities [25]. Furthermore, studies in monkeys showed that neutralizing antibodies are generated by the primary infection of SARS-CoV-2 that could protect monkeys from re-infection [26]. Similarly, recent studies showed that passive

transfer of neutralizing antibodies from treated patients of SARS-COV to infected patients decreased viral load and mortality in patients [27]. Transfusion of COVID-19 convalescent plasma (CCP) is suggested that use either as a therapy for patients with laboratory-confirmed COVID-19 or as prophylaxis for prevention of COVID-19 disease in a high-risk population. However, most of the current clinical trial studies performed on adult patients with moderate COVID-19 disease who not required to hospitalization and severe COVID-19 disease who required mechanical ventilation [28]. Duan *et al*. had shown infusion of 200 ml of convalescent plasma containing viral neutralizing antibodies with titers more than 1:640 to 10 patients with COVID-19 improved their clinical symptoms and decreased CRP level in all patients [29]. Importantly, following the onset of COVID-19, antibodies appeared in sera with an average time of 12 and 14 days for IgM and IgG, respectively. The presence of antibodies in the first 7 days of the COVID-19 disease was less than 40%, then at day-15 following the onset of disease, titers of antibodies elevated to 79.8% and 94.3% for IgG and IgM, respectively. It should be mentioned that the third week after the onset of the disease is appropriate for collecting convalescent plasma with high titers containing neutralizing antibodies against SARS-CoV-2 [30]. This has been suggested that two units of 200–250 ml of ABO-compatible convalescent plasma be transferred to each patient weighing 50 and 80 kg at early-on, and up to day 10 after disease onset, and also infusion rate should be slow and under special care to identification adverse effects [27]. However, different doses, between 200–600 ml per adult patient, and times of COVID-19 convalescent plasma transfusion are under investigation in clinical trials. Likewise, most studies have suggested the use of 1–2 doses of 200 ml for severe COVID-19 patients, as well as the viremia peak, is observed at the first week of infection and is recommended the COVID-19 convalescent plasma has been better to use at early of disease before the innate immune cells migration and inflammatory cytokine storm starts. Several studies on using of convalescent plasma showed improving clinical symptoms such as reduced fever, reduced pulmonary lesions, improved lymphocyte count, decreased viral load and increased IgM, IgG and neutralizing antibody titers [28].

Recent therapeutic use of convalescent sera on a large scale analysis of patients with severe or life-threatening COVID-19 indicated that after convalescent plasma transfusion in 5000 patients, the rate of serious adverse effects was less than 1% at first four hours and the seven-day death rate was 14.9%. Therefore, convalescent plasma transfusion is safe in severe COVID-19 patients [31].

2.3.2. Intravenous immunoglobulin (IVIG) therapy

Intravenous immunoglobulin (IVIG) prepared from the pooled serum of 1000 and 15,000 healthy donors. In the past decades, IVIG therapy induced passive immunity with anti-inflammatory and immunomodulatory effects. Some randomized clinical trials on the efficacy of IVIG in severe COVID-19 have been started. In an open-label trial study identified that IVIG therapy (0.4 g/kg for 5 days) ameliorated clinical symptoms in three patients with life-threatening COVID-19. IVIG blocks the activation and release of inflammatory cytokines from innate immune cells, inhibits Th1 and Th17, which are involved in inflammation, probably enhances regulatory T (Treg) cells as an immune suppressor cell for decreasing inflammation, which is indicated a significant reduction in the number of peripheral blood Treg cells in severe cases of patients with COVID-19 [21,32]. A retrospective study has been shown that IVIG therapy on 58 severe or critically ill cases of COVID-19 during the first 48 hours of hospitalization decreased hospital stay and ventilator use and improved clinical symptoms [33].

2.4. Immunotherapy based on Natural killer (NK) cells

The total number of NK cells and cytotoxic T cells was reduced in COVID-19 patients. On the other hand, the down-regulation of NKG2A expression, as an inhibitory marker, on NK cells was correlated with clearance of SARS-CoV-2 infection. In other words, the exhausted phenotype of cytotoxic lymphocyte cells is correlated with high expression NKG2A on cells and disease progression. These data could suggest targeting NKG2A to improve cytotoxic immune responses against SARS-CoV-2, as well as other immune checkpoint inhibitors such as anti-TIGIT and anti-PD1, which helped restore the immune responses of exhausted NK and T cells in the context of cancer [34]. Because of the antiviral activity of NK cells, several cell therapies based on NK cells are under consideration.

The first cell-based immunotherapy has been permitted by the FDA for clinical investigation of an allogeneic, off-the-shelf, and cryopreserved NK cells made by Cellularity (CYNK-001) for COVID-19 patients. CYNK-001 contains $CD56^{+}$ $CD3^{-}$ NK cells derived from human placental hematopoietic $CD34^{+}$ stem cells. A Phase I/II Study of CYNK-001 infusion in adults with COVID-19 is an ongoing trial (ClinicalTrials.gov Identifier: NCT04365101) that in phase I will assess the efficacy and safety of infusion of CYNK-001 (at days 1,4 and 7) in 14 eligible patients with mild to moderate COVID-19, and in phase II will use the randomized and open-label design of multiple doses infusion of NK cells derived from placental $CD34^{+}$ cells in 72 patients and will be compared to the control group [35].

Furthermore, in phase I/II randomized clinical trial study (ClinicalTrials.gov Identifier: NCT04324996) is currently being tested intravenous infusion of engineered NK cells derived from umbilical cord blood, is called NKG2D-ACE2 CAR-NK cell, in 90 eligible patients with mild to severe COVID-19 disease. These cells secret IL-15 which is required for the long-term survival of NK cells, and also release a single-chain variable fragment (scFv), which binds GM-CSF to prevent cytokine release syndrome (CRS). Moreover, these engineered cells express NKG2D receptors (activating receptors) and ACE-2 (receptor of SARS-CoV-2 spike proteins). Therefore, these cells can competitively prevent SARS-CoV-2 infection through ACE-2 expression, and thus NKG2D-ACE2 CAR-NK cells can clear virus-infected cells as well as unbound SARS-CoV-2 virions with a favorable safety profile [21,36].

2.5. Mesenchymal stem cells (MSCs) therapy

Mesenchymal stem cells (MSCs), due to their immunomodulatory and anti-inflammatory capabilities is another candidate for cell-based therapy which is introduced for COVID-19 therapeutic options. Probably, MSCs therapy prevents cytokine storm through secretion of immunomodulatory factors or direct interaction with immune cells [37]. Moreover, after transplantation of MSCs, these cells improve the lung function of patients with COVID-19 by triggering endogenous repair and recovering the pulmonary microenvironment due to their regenerative traits [38]. A recent case report from China showed that human umbilical cord MSC (hUCMSC) intravenous infusions (5×10^7 cells for three times), successfully modulated the immune response and restored the injured tissue of a 65-year-old female critically ill COVID-19 patient without side effects [39].

According to Leung and colleagues on a pilot clinical trial study, a single intravenous infusion of MSCs transplantation (1×10^6 cells/Kg of weight) could improve the pulmonary function of 7 enrolled with confirmed COVID-19 pneumonia, and no adverse effects were observed. Importantly, the level of inflammatory cytokines were decreased whereas IL-10 increased, and also peripheral regulatory lymphocytes and regulatory dendritic cells ($CD14^+$ $CD11c^+$ $CD11b^{mid}$) were increased after MSCs transplantation [40]. Thus, it appears immunomodulatory traits of MSCs are caused that MSCs therapy probably is a proper candidate for investigation of treatment (clinical trials or combinational therapy) for COVID-19 patients [38].

3. Conclusion

Despite different studies to fight COVID-19, there has not been any approved specific vaccine or curative anti-viral drug until now. Immunotherapies therapeutics may have a protective effect against COVID-19; they are based on neutralizing monoclonal antibodies that inhibit virus entry, inflammatory cytokine neutralization that prevents cytokine storm, passive immunotherapy, cell therapy based on NK cells and immunomodulatory effect of Mesenchymal stem cells therapy. Further studies are needed to check the exact efficacy of immune-based therapies in COVID-19.

Funding

This paper is not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial relationships or otherwise to disclose.

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