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MINI REVIEW

Immunotherapies and immunomodulatory approaches in clinical trials - a mini review

Mohd. Iqbal Yatoo[a], Zeenat Hamid[b], Izhar Rather[a], Qurat Ul Ain Nazir[a], Riyaz Ahmed Bhat[a], Abrar Ul Haq[a], Suhail Nabi Magray[c], Zulfqar Haq[d], Ranjit Sah[e], Ruchi Tiwari[f], SenthilKumar Natesan[g], Muhammad Bilal[h], Harapan Harapan[i,j,k], and Kuldeep Dhama[l]

[a]Division of Veterinary Clinical Complex, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, Alusteng Srinagar, Sher-E-Kashmir University of Agricultural Sciences and Technology of Kashmir, Shalimar, Jammu and Kashmir, India; [b]Department of Biotechnology, University of Kashmir, Jammu and Kashmir, India; [c]Division of Animal Biotechnology, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, Alusteng Srinagar, Sher-E-Kashmir University of Agricultural Sciences and Technology of Kashmir, Shalimar, Jammu and Kashmir, India; [d]ICAR-Centre for Research on Poultry, Division of Livestock Production and Management, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, Alusteng Srinagar, Sher-E-Kashmir University of Agricultural Sciences and Technology of Kashmir, Shalimar, Jammu and Kashmir, India; [e]Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Nepal; [f]Department of Veterinary Microbiology and Immunology, College of Veterinary Sciences, UP Pandit Deen Dayal Upadhayay Pashu Chikitsa Vigyan Vishwavidyalay Evum Go-Anusandhan Sansthan (DUVASU), Mathura, Uttar Pradesh, India; [g]Department of Infectious Diseases, Indian Institute of Public Health Gandhinagar, Gandhinagar, Gujarat, India; [h]School of Life Science and Food Engineering, Huaiyin Institute of Technology, Huaian, China; [i]Medical Research Unit, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia; [j]Tropical Disease Centre, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia; [k]Department of Microbiology, School of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia; [l]Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, Uttar Pradesh, India

ABSTRACT

The coronavirus disease (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created havoc worldwide. Due to the non-availability of any vaccine or drugs against COVID-19, immunotherapies involving convalescent plasma, immunoglobulins, antibodies (monoclonal or polyclonal), and the use of immunomodulatory agents to enhance immunity are valuable alternative options. Cell-based therapies including natural killer cells, T cells, stem cells along with cytokines and toll-like receptors (TLRs) based therapies are also being exploited potentially against COVID-19. Future research need to strengthen the field of developing effective immunotherapeutics and immunomodulators with a thrust of providing appropriate, affordable, convenient, and cost-effective prophylactic and treatment regimens to combat global COVID-19 crisis that has led to a state of medical emergency enforcing entire countries of the world to devote their research infrastructure and manpower in tackling this pandemic.

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Introduction

The lack of specific antivirals against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) limits the efficacy of the various drugs being used to treat patients with the coronavirus disease (COVID-19). Numerous therapeutics are being explored for treatment of COVID-19 with few having relevance while most of the others being nonspecific and hence non-effective and less safe.[1–6] Immunotherapy is a novel approach for the treatment of diseases by manipulating patients own immune system. It is a rapidly advancing field of translational science and it has been recognized as breakthrough of the year 2013 by the journal Science.[7] Immunoglobulin therapy, convalescent plasma therapy,[8,9] antibodies, monoclonal antibodies (mAbs),[10] natural killer (NK) cell-based therapies,[11] T cell-based therapies,[12] Toll-like receptors (TLRs),[13,14] cytokine therapies[15,16] and immune modulators are some of the immunotherapeutic options available and few of them are being explored for treatment of COVID-19.[17–21] The only specific treatment option available for the disease currently is believed to be the use of convalescent plasma from patients who have recovered from COVID-19.[22,23] This plasma is readily available currently because many patients have recovered from COVID-19, and thus, can donate their plasma.[22,24] This is a passive immunization method of disease prevention since the immunoglobulins in the plasma can either directly inhibit the infectious agent, SARS-CoV-2, through viral neutralization or by antibody-dependent cellular cytotoxicity and/or induction of phagocytosis,[24] and numerous cellular mechanisms can be involved in this therapy.[25] However, there are conflicting results in some recent clinical trials that warrant proper evaluation of plasma therapy in COVID-19.

Hence, in addition to plasma therapy,[9,26,27] synthesized antibodies[28] preferably neutralizing monoclonal antibodies,[29,30] and interferons[26] have a potential to be utilized as immunotherapeutics in COVID-19 cases. Antibody-based immunotherapeutics including intravenous immunoglobulins, and mAbs are well

CONTACT Mohd. Iqbal Yatoo iqbalyatoo@gmail.com Division of Veterinary Clinical Complex, Faculty of Veterinary Sciences and Animal Husbandry, Shuhama, Alusteng Srinagar, Sher-E-Kashmir University of Agricultural Sciences and Technology of Kashmir, Shalimar, Srinagar-190006, Jammu and Kashmir, India; Kuldeep Dhama Indiakdhama@rediffmail.com Division of Pathology, ICAR –Indian Veterinary Research Institute, Izatnagar 243122, Bareilly, Uttar Pradesh.

known for safety and efficacy over decades as many are already in use for treating various cancers and some are being used for COVID-19 treatment recently.[21]

Immunomodulation and cell-based immunotherapies are other possible approaches being suggested or under consideration in COVID-19 along with molecule-based immunotherapy.[12,20] These immunotherapeutic avenues are being explored for managing the current pandemic crisis, however, for long-term protection and future prevention, vaccines will be imperative.[31] Immunotherapy is a rapidly evolving field that holds potential novel therapies for cancers, autoimmune disorders, and infectious diseases. The present review gives a brief account of promising immunotherapies and immunomodulatory approaches to combat SARS-CoV-2/COVID-19.

Immunotherapies for COVID-19

Currently, the conventional polyclonal antibody-based immunotherapeutic products such convalescent plasma, fractionated plasma, purified immunoglobulin are already in use for treating COVID-19 patients.[8,10,19,21] Few of the antibodies such as tocilizumab and itolizumab are used for treating COVID-19 patients under emergency use authorization. In the next phase, novel therapeutic monoclonal antibodies will likely be available for treating COVID-19 as many such products are at different stages of development.[21,32] Apart from antibody-based immunotherapies, the cellular immunotherapy is also used for treating various diseases. The living immune cells are recognized as therapeutic drugs. Both US FDA and EMEA has approved autologous cell-based immunotherapeutic products for treating cancers.[33,34] The cellular immunotherapy takes advantage of activated immune cells including Dendritic cells, Natural killer (NK) cells, T-cells for the treatment of diseases and are also being exploited against SARS-CoV-2.[11,12,20] The T cell-based approaches hold promising future for treating COVID-19.

Modulating immune response against SARS-CoV-2 through immunomodulators is also being explored with cytokines, TLR agonists, herbal and synthetic compounds being under consideration. They can regulate cellular or humoral immunity against SARS-CoV-2, prevent inflammatory cascade by modulating cytokine storm when most of the mechanisms are yet to be explored.[13–21]

These novel immunotherapeutic approaches against SARS-CoV-2 have prospects in therapy of COVID-19 hence require a brief description about current scenario, applications, limitations, and future possibilities.

1. Convalescent plasma and antibody therapy

1.1 Convalescent plasma (CP) and Immunoglobulins

Plasma therapy can elicit a rapid response and provide immediate relief to the patient, and does not require additional time for immunity development, as is needed for vaccination. Convalescent plasma therapy has minimized disease severity and reduced mortality in COVID-19 cases in previous studies however future studies will reveal the safety and efficacy.[27,35] This method can also be used as a preventive measure for high-risk groups such as healthcare providers, family members of affected patients, and personnel working in quarantine facilities.[24]

Convalescent plasma therapy particularly that obtained from recovered patients, is thus being considered as the specific therapy.[24] Use of convalescent plasma can inhibit the attachment of the virus spike protein with the host ACE2 receptor on targeted cells and lysis of the virus through antibody-mediated opsonization or complement activation.[25] Shen et al.[36] and Duan et al.[37] used convalescent plasma to treat COVID-19 patients. Following plasma therapy, viral loads decreased, neutralizing antibody titers increased, and acute respiratory distress syndrome (ARDS) resolved in 12 days, at which time most patients ceased to show symptoms, and patients were discharged within 2 months.[36] A dose of 200 mL of convalescent plasma was well tolerated and significantly increased or maintained the neutralizing antibodies at a high level, leading to the disappearance of viremia in 7 d, resolution of clinical symptoms, and paraclinical criteria within 3 d, and resolution of radiological lung lesions within 7 d.[37] Zhang et al.[27] have also explored convalescent plasma therapy and reported a decrease in disease severity, mortality (4 out of 5 survived), and viral load (decreased from 55×10^5 to 3.9×10^4 to 180 copies per milliliter) in COVID-19 patients; however, they recommend an evaluation of the safety and efficacy of this kind of therapy. This can be achieved via the use of specific antibodies developed against SARS-CoV-2.

Immunoglobulin therapy using human convalescent sera obtained from patients recovering from COVID-19 for treatment and prevention has been reviewed.[24] Convalescent plasma or immunoglobulins help in minimizing clinical signs such as cough, pneumonia, fever, and improve oxygen saturation and recovery,[38] hasten resolution of lung infiltration pathology,[38] stabilize inflammatory mediators (decrease CRP and IL-6), and leukocytosis and lymphopenia,[38] lower viral loads, improve survival, reduce hospital stay and reduce mortality without any adverse side effect.[9] The value of cycle threshold (Ct) of ORF1b gene in rRT-PCR changed from 20.51 to 24.98 on day 5–10 to 33.96–36.33 on day 9–20 after plasma infusion in COVID-19 patients and became negative by day 20–26.[38] The possible explanation could be that convalescent plasma contains antibodies that neutralize viruses.[25,30] This neutralization of virus by CP-antibody can be due to prevention of replication (e.g., by complement activation or phagocytosis) or by binding without hindering replication.[39,40] Efficacy of convalescent plasma therapy depends on antibodies present in this plasma, that determine the suppression of viremia through improved clearance of viruses, blocking of new infections, in addition to clearance of infected cells.[41,42] Convalescent plasma or immunoglobulins may suppress viruses, lower viremia, remove or clear infection, block new infection, and clear-infected cells.[9,41] It hastens reduction of viral load irrespective of time of therapy earliest being more beneficial.[28,38] It maintains high antibody titer till immune response develops, and provides protection.[28] In viral diseases, viremia peaks within the first week of the infection, and immune response is elicited by day 10–14, thereafter viral clearance begins.[43–46] Immunoglobulin concentration peaks at

convalescent stage[28] and should be collected within 2 weeks of recovery for obtaining high neutralization antibody titer.[47] It resolves histopathological alterations in lungs.[42,48]

A few studies on COVID-19 patients have reported on clinical application and possible therapeutic potential of convalescent plasma.[9,22,23,49] Intravenous immunoglobulin therapy administered to patients with COVID-19 gave good results in terms of recovery and minimization of disease severity. The use of intravenous immunoglobulin helps in increasing the anti-infection potential, especially in severely affected patients, but the efficacy of the therapy needs further evaluation.[9,50] Intravenous immunoglobulins are administered at a dose rate of 1.0 g/kg/day for 2 days or at 400 mg/kg/day for 5 days.[9] Immunoglobulins can be used in severe cases of COVID-19, but with certain precautions.[27] In one clinical study, of the 46 patients administered intravenous immunoglobulin therapy, 10 survived.[30]

In the case of COVID-19, the mechanism of action of passive antibody therapy that is being predicted is viral neutralization; however, other mechanisms are anticipated, such as antibody-dependent cellular cytotoxicity and phagocytosis. For COVID-19, possible source of antibodies are human convalescent sera from recovered patients of COVID-19, mAbs, or animal host-derived preparations (e.g., genetically engineered cows producing human antibodies).[51] COVID-19 convalescent sera could be a satisfactory option in the treatment of individuals with early symptoms and prevent disease in those exposed. In convalescent serum administered patients, scientists are predicting that it will prevent SARS-CoV-2 infection. If researchers confirm this prediction, convalescent sera administered patients may not require quarantine. The use of convalescent serum would be a temporary solution that could be used under the prevailing circumstances of deadly disease.[24]

Convalescent plasma is being administered to critical COVID-19 patients for therapeutic purposes; however, it can be used in less severe cases or risk groups to reduce the severity or prevent the occurrence of disease. Parameters, such as clinical signs, biomarkers (hematological, biochemical, and inflammatory), lung pathology, radiological data, viral load, viral clearance, antibody levels, cure rate, recovery period, and mortality/fatality rate, are being evaluated in the clinical trials on convalescent plasma.[47] A dose of 500 ml is administered over 12 hours at an intravenous infusion rate of 250 ml/h.[38] Intravenous administration of immunoglobulins can aid the prevention of SARS-CoV-2-induced pulmonary inflammation in the respiratory tract by blocking FcR activation.[29,52,53] Antibody 47D11 (human) was the first reported to neutralizes SARS-CoV-2.[54] It binds on a conserved epitope on RBD of spike protein and neutralizes SARS-CoV-2.[5,10] The 47D11 (human) mAb can neutralize SARS-CoV-2 by targeting the conserved epitope on the spike protein, specifically, the core structure of the S1B receptor binding domain of S protein.[54] Tian et al.[55] suggested that the mAbCR3022 effectively neutralizes SARS-CoV-2 at a concentration of 23.5 μg/ml and can be used as a potential therapeutic, alone or in combination with other neutralizing antibodies, for the prevention and treatment of SARS-CoV-2 infections.

Limitations of convalescent plasma include difficulty in procurement, adverse reactions, anaphylaxis, pulmonary edema, and nonspecificity;[38,40] a few other concerns can be transmission of serum disease and antibody-dependent enhancement of infection[10,24] as well as short-term immunity.[8] The future prospects include recommendation by WHO[56] and NHC.[57] Currently, it is the immediate therapy available. Accumulating evidence suggests that convalescent plasma from recovered patients can be used as therapy without adverse side effects; however, proper evaluation is warranted for safety and efficacy purposes.[9,42] A large number of patients are recovering, and thus huge quantity of convalescent plasma can be obtained.[40] Large-scale clinical evaluation is required for safety and efficacy testing. Therefore, dose standardization, amelioration of confounding effects of other conjoint therapeutics, proper designing of clinical trials, and exploration of specific modalities are essential.

Despite the benefits of convalescent plasma and immunoglobulins, some limitations need to be kept in mind. The chances of the risk of infection via convalescent plasma need to be minimized. The protection conferred by plasma therapy is not long-lasting, and repeated infusion is required depending on the amount and composition.[24] As per NIH there are insufficient data available to recommend convalescent plasma for treatment of COVID-19 or against it (NIH 2020).[58] Immunoglobulins are effective against infectious inoculums at the peak stage at the onset of clinical signs, but not following a delay of even a few days. They may counter inflammatory responses at the early stages. Immunoglobulins are more effective as prophylactics than as therapeutics. Further administration of immunotherapeutics may compromise the natural immunity of patients, thus rendering them susceptible to future infection; however, early experimental studies have suggested that a considerable immune response is mounted.[59] There is a risk of abnormal reactions such as thrombotic events,[60] pulmonary edema, and antibody-dependent enhancement (ADE).[61] The availability and production of convalescent plasma is meager. These are non-specific. Specific monoclonal antibodies can ameliorate some of these disadvantages,[29] and production in genetically engineered animals can boost availability.[24] Some companies have initiated the production of high-concentration-purified immunoglobulins; Takeda being one among them.[24,62] A lack of high-quality studies and an adequate antibody titer should be accounted for further approval. Ethical production and controlled conditions must be maintained.[60]

1.2 Monoclonal antibodies

Monoclonal antibodies (mAbs) against SARS-CoV-2 with specificity for the virus[55] have been reviewed by Shanmugaraj et al.[29] Several mAb such as bevacizumab, sarilumab, adalimumab, camrelizumab, eculizumab, mepolizumab, PD-1 mAb, and tocilizumab are being evaluated as therapy for COVID-19.[31,56,63] Targeting SARS-CoV-2 structures such as the S1 subunit of the spike glycoprotein can help in the production of mAbs that will be specific, effective, and easy to produce for COVID-19 treatment.[55,64]

mAbs are specific and minimize adverse effects of convalescent plasma.[29] They can shorten the course of infection and

protect uninfected cells exposed to SARS-CoV-2.[10] They can block or neutralize coronavirus.[32]

Bevacizumab is a recombinant-humanized mAb targeting vascular endothelial growth factor (VEGF) and has been used clinically for more than 16 years. A clinical trial suggests that bevacizumab may be effective in patients with COVID-19 pneumonia.[65] This mAb may reduce the levels of VEGF caused by severe inflammation, thereby suppressing edema in patients with COVID-19.[63,65] Sarilumab, a human mAb that targets interleukin-6 receptor,[66] has recently been evaluated in a clinical trial for COVID-19 patients.[67] It is being promoted by Sanofi and Regeneron Pharmaceuticals.[68] Other mAbs currently used together with protease inhibitors are under clinical trials; these include adalimumab, camrelizumab, eculizumab, mepolizumab, PD-1 mAb, and tocilizumab.[69] Gimsilumaba mAb targeting granulocyte macrophage-colony stimulating factor (GM-CSF), believed to be a key driver of lung hyper-inflammation, is being evaluated by researchers at Temple University Hospital, USA[70] for potential ameliorative effect on lung injury or ARDS. In addition to potential therapeutic effects, the dosage, safety, and efficacy of these mAbs also need to be determined before they can be used clinically. With respect to clinical application, Shen et al.[35,36] reported the infusion of SARS-CoV-2–specific IgG having a binding titer > 1:1000 and neutralization titer >40 after 10–22 days of admission. B38, H4, and 47D11are the specific mAbs against COVID-19 and have prospects for being effectively used.[32] However, some have not been effective in recent clinical trials e.g. tocilizumab (Stone et al., 2020).[71] Recently, nanobodies have been speculated for application in COVID-19.[72] They are antigen-binding domains found in camelid species and are having only heavy chains, no light chains. They have compact structure, lower molecular weight, the smallest active antigen-binding fragments, better stability, and better penetration/bioavailability due to small size.[72] There are some limitations in monoclonal antibody based therapy including production limits, costs, and time involvement.[32] However, novel methods of production can overcome some of these limitations like expression systems in plants.[32]

2. Cell-based therapies

2.1 Natural Killer (NK) cell-based therapies

NK cells have been suggested as one possible therapeutic approach against COVID-19.[11] Their antiviral and regulatory functions may play important role in COVID-19 related immune dysfunction and cytokine storm.[67] Activation, immunotyping, reduction in number of circulating NK cells, alteration in subsets and exhaustion in phenotypes following coronavirus infection indicates their involvement in immunopathology of COVID-19.[73,74] As exaggerated inflammation is hall mark of COVID-19 severity[75] and NK cells have prominent role in inflammatory cascade hence immunomodulation by NK cells can prove beneficial for COVID-19 patients.[11,74] In one clinical trial, application of NK cells for treatment of COVID-19 patients has evaluated safety and efficiency of NK cell therapy in combination with standard therapy.[76] Improvement in clinical parameters (temperature), clinical signs (respiratory distress), decrease in adverse events and decrease in time of negative test, improvement in CD4+/CD8 + counts, pathological lesions in lungs and decrease in mortality have been noted. Hence modulation of NK cell activity can help in combating COVID-19. Imiquimod, an imidazoquinolines compound, can stimulate NK cells hence has prospects for therapeutic application in COVID-19.[14]

2.2 T cell-based therapies

T cell-based therapies are being evaluated against novel corona virus. CD4+ CD25+ FoxP3+ regulatory T-cell (Treg)-based strategies can balance dysregulated immune response in COVID-19.[77] These therapies are also proving as successful therapeutic option in patients of hematological malignancies.[78,79] Patients suffering from relapsed/refractory (R/R) malignant diseases are unavoidably affected due to COVID-19 and to counter this medical insult, chimeric antigen receptor T-cell (CAR-T) therapy is underway with good results.[80,81] Two anti-CD19 CAR T-cell products axicabtagene ciloleucel (Brand name: Yescarta) and tisagenlecleucel (Brand name: Kymriah) are currently accepted by the United States Food and Drug Administration (FDA) for treatment in COVID-19 patients.[12] In previous studies it has been reported that donor-derived virus-specific T cells (CD8) show good results in immune-compromised patients infected with virus.[82,83] In Singapore, only one clinical study has reported the efficacy of adoptive cell therapy with SARS-CoV-2-specific T cells in severely diseased patients.[83,84] Grifoni et al.[85] have projected to use SARS-CoV-2-specific and HLA-matched cytotoxic T cells arranged from convalescent COVID-19 patients as need of the hour therapy in COVID 19 patients and interestingly, SARS-CoV-2-specific CD8 T cells have been identified in approximately 70% of corona positive convalescent patients. Braun et al.[86] has also noted higher proportion of SARS-CoV-2 spike glycoprotein (S)-reactive CD4 + T cells in infected cases (83%) compared to healthy cases (35%). It's reported that use of HLA-E-restricted CD8 T cells helps to improve T cell immunotherapy in COVID-19 patients by immediately killing infected cells and reducing intracellular infections, additionally it can reduce the degree of the inflammatory response and minimize collateral tissue damage, which is a significant element in the pathogenesis of SARS-CoV-2. HLA E restricted CD8 T cells will not cause immune rejection thus making these cells more suitable for T cell therapies. Scientists believe that HLA-E-restricted and SARS-CoV-2-specific CD8 T cells may perhaps be quickly and cost effectively arranged in huge numbers from COVID-19 donors that can be then stored and used in severely affected individuals.[83]

2.3 Chimeric Antigen Receptor (CAR) T cell therapy

Prospects of CAR T cell therapy need to be evaluated in COVID-19 since cell-based therapies in COVID-19 patients with malignancies have many challenges.[12] Most recently, the genetically engineered CAR T cell therapy has been approved by US FDA for the use in cancer patients.[87] Safety and efficacy of CAR T cell therapy has been well proven through large number of clinical trials. Approved CAR T cell therapies Tisagenlecleucel (Kymriah™) and Ciloleucel (Yescarta™) are used for treating specific types of leukemia and lymphoma. In

CAR T-cell therapy, blood is taken from a patient and processed in the laboratory to express a specific chimeric antigen receptor on their surface. CAR is a combination of the single-chain fragment variable (ScFV) sequence of the monoclonal antibody, a transmembrane domain, and the intracytoplasmic signaling domain of CD3 zeta chain. The CAR gene is introduced into the T cells using viral vectors and then multiplied in the laboratory and given back to the patient through an intravenous infusion.[88–90] The idea of using CAR/TCR-T cell therapy has been proposed for treating chronic viral infections such as HIV and hepatitis B.[91] Researchers at Duke-NUS Medical School in Singapore are exploring the possibility of CAR T cells against COVID-19.[92] Bishop[93] emphasized the need of optimizing CAR T-cell therapy during the COVID-19 pandemic for obtaining desired results. The CAR T cells specific for the viral surface antigens can be generated and it can be used for specific killing of viral-infected cells and prevent further spread of infection within the body. Antigen-specific CAR T cells can also be used as therapeutic vaccines. Hu et al.[79] pointed out CAR T-cell treatment as an extraordinarily challenging during the COVID-19 pandemic while emphasizing many medical and technical factors to be taken into consideration before, during, and after CAR-T therapy. The important resources required for successful CAR T cell therapy include apheresis and cell processing laboratory, shipping/logistics, manufacturing, ICU capacity, blood bank, laboratory testing, radiology, pathology, caregiver and housing managing some of which during COVID-19 have caused disruption in cell-based therapies.[12] Unfortunately, there are some toxicity issues related to CAR T cell therapy including prolonged cytopenias, cytokine release syndrome (CRS), and neurotoxicity that need to be addressed.[12,78,94–97]

2.4 Stem cell therapy

Stem cell therapy has found prospects for application in COVID-19.[20,98] Numerous clinical trials involving stem cells either alone or in combination with other therapeutic modalities are under investigation.[20] To explore the significant immunomodulatory effect of mesenchymal stem cells, it was used in seven COVID-19 pneumonia patients in Beijing YouAn Hospital, China. The clinical results, as well as changes in inflammatory factors and immune function along with adverse effects, were measured for 14 days after mesenchymal stem cell inoculation. There was an improvement in lung function and symptoms in the seven enrolled patients within 2 days after MSC transplantation. Among these patients, two common and one severely affected patient recovered and was discharged in 10 days after stem cell therapy. Laboratory evaluation revealed an increase in peripheral lymphocyte levels, decrease in C-reactive protein levels, and absence of highly activated cytokine-secreting immune cells, such as CXCR3 + CD4 + T cells, CXCR3+ CD8 + T cells, and CXCR3+ NK cells, in 3–6 days. Moreover, there was a considerable decrease in TNF-α levels, but an increase in IL-10 levels in the MSC treatment group, compared to the placebo control group. Gene expression profile revealed MSCs as ACE2 and TMPRSS2, which indicated that MSCs were free from COVID-19 infection. Therefore, this therapy proved to be safe and successful for COVID-19 pneumonia patients.[99] A recent clinical trial[100] is underway, in which human menstrual blood-derived stem cells are being infused intravenously to treat acute COVID-19 pneumonia.

3. Immunomodulator therapy

3.1 Toll-like receptors (TLRs)

Agents acting on TLR receptors are finding role in COVID-19 therapy as they are the involved in modulating innate immunity.[14,101] Targeting TLRs can help in treatment or protection from COVID-19.[102] For RNA viruses, TLRs 3, 7, and 8 are important pattern recognition receptors (PRRs) that help in signaling cascade through pathogen-associated molecular patterns (PAMPs) inducing expression of transcription factors resulting in production of interferons which are essential for antiviral defense.[14] Imiquimod helps in TLR7 activation, stimulation of specific and nonspecific immune response and cytokine production, thus can be helpful in COVID-19 therapy.[13,14] TLR5 helps in activation of innate immunity and stimulation of TLR5 through bacterial flagellin, can help in early modulating of immune response against COVID-19, thus can have therapeutic or prophylactic applications.[103]

3.2 Cytokine therapies

Cytokines play an important role in COVID-19 pathobiology.[16] They are involved in inflammatory cascade wherein exaggeration may lead to cytokine storm usually noticed in severe cases of COVID-19.[15] Alteration in levels of interleukin (IL)-2, IL-7, IL-10, tumor necrosis factor (TNF), granulocyte-colony stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10; CXCL10), MCP-1 (CCL2) and MIP-1A (CCL3), IL-1, IL-1ra, IL-2 R, IL-6, IL-8 (CXCL8), IL-17, interferon (IFN)-γ and GM-CSF (granulocyte-macrophage colony-stimulating factor) have been noted in COVID-19 patients.[16] Hence modulating levels of these cytokines/chemokines is essential for therapeutic regimes as has been observed for other diseases.[104] Tocilizumab and sarilumab block IL-6 receptors and have been used in treatment of COVID-19 patients.[105] Ruxolitinib, a JAK–STAT inhibitor that targets IFN- γ, has been used in COVID-19 therapy.[106] Adalimumab, etanercept, and golimumab are the TNF blocking antibodies and have been used in treatment of COVID-19 cases.[107] Though blocking proinflammatory mediators may virtually prevent inflammation but for anti-inflammatory mediators like IL-10 over-activation or ablation need to be clarified. Also continuous use of immunosuppressants may lead to adverse effects like chronic inflammatory disorders.[16]

Wang et al.[5] and NHC[57] have recommended antiviral therapies with atomized inhalation of α-interferon following conventional therapy. The α-interferon atomization inhalation can be administered at a dose rate of 5 million U per time in sterile injection water, twice a day, for adults.[26] Shen et al.[35] have also recommended the use of interferon-α as an antiviral and suggested that interferon-α can be administered in two forms, interferon-α nebulization and interferon-α2b spray.[35] Interferon-α nebulization is used at a dose rate of 200,000–400,000 IU/kg or 2–4 μg/kg in 2 mL sterile water,

nebulization is used two times per day for 5–7 days, and interferon-α2b spray is used at 8000 IU, once every 1–2 hours, 8–10 sprays/day for a course of 5–7 days with 1–2 sprays on each side of the nasal cavity, and 8–10 sprays on the oropharynx.[35] Interferon-α2b has been suggested as a treatment option for patients for COVID-19 along with supportive care, isolation, oxygen therapy, fluid management, and administration of antimicrobials to monitor microbial infections.[50,56,108] These alternate therapies may overcome limitations associated with other conventional therapies being used under emergency authorization however this may require proper evaluation.[24,109,110]

3.3 Immune modulators

Immune modulation is believed to be an important option for avoiding complications of SARS-CoV-2 infection and treating COVID-19 patients, hence immunomodulatory agents thus can prove highly beneficial in management of COVID-19 disease during current pandemic.[17,111–113] As there is hyper-inflammation and hyper-activation of immune system leading to cytokine storm in COVID-19, therefore immunosuppressants have been recommended in treatment of COVID-19.-[113,114] However, prolonged immunosuppression can lead to severe infection hence modulation of immune response in a balanced manner is prerequisite and thus immunomodulators can play an important role for such situation.[113] Innate immunity has a pivotal role in prevention and treatment of COVID-19, however aggravation can produce detrimental effects[115,116] including immune hyperactivation and acute respiratory distress syndrome.[113] Modulating innate immunity and developing trained immunity can help in harnessing antiviral immune response.[113,115,116] In the initial stages during incubation phase or in asymptomatic cases, host immunity is important for antiviral defense and can be supplemented with anti-sera or pegylated IFNα.[117] In the later phase of infection or symptomatic cases, aggravated inflammation and immune response requires immunomodulation.[117] As Th1 immunity is the main antiviral mechanism in the body compared to Th2 hence maintaining adequate Th1 immunity is important for combating SARS-CoV-2 infection, however a balance between Th1 and Th2 immune response is essential for preventing aggravation of immune response.[118] Low Th1 immunity in some sections of population including malnutritioned, overcrowded, and vitamin D deficient groups has been speculated as a reason of severity and higher morbidity and mortality in these groups;[118] hence require immunomodulatory interventions. Hence, immunity and immunomodulators may have role in COVID-19 prevention or management.[119–121]

Some pathological studies on pulmonary edema and hyaline membrane formation suggest that the use of immunomodulators together with ventilator support helps in preventing the development of acute respiratory distress syndrome (ARDS). Recently, a trial was conducted to check the efficacy of fingolimod in COVID-19 patients.[122] Each patient in the fingolimod treatment group received 0.5 mg of fingolimod orally once daily, for three consecutive days. Thalidomide is classified as an immunomodulatory agent and has clinically been reported to be used in combination with antiviral drugs along with some other conventional therapies. In previous studies, it has achieved satisfactory results in the treatment of lung injury caused by H1N1. Considering these facts, clinical trials have been conducted using thalidomide against COVID-19 lung injury patients. Thalidomide speeds up the degradation of messenger RNA in blood cells thereby inhibiting viral replication.[123,124]

Dietary intake of balanced foods along with nutritional supplements including vitamins, trace elements, probiotics, herbs, and nutraceuticals have been proposed to be effective for COVID-19 due to their potent role in immune functioning and acting as immunity boosters.[125,126] Various phytochemicals/phytocompounds present in medicinal herbs have shown proven immunomodulatory and antiviral potentials, and are presently being exploited for their prophylactic and therapeutic values in management of COVID-19 patients.[4,127–135] These include *Withania somnifera* (Indian ginseng, Ashwagandha),[136–138] *Curcuma longa* (curcuma/turmeric),[130,138] *Allium sativum* (garlic),[132] *Camellia sinensis* (green tea),[139] *Glycyrrhiza glabra* (licorice),[130,133,140] *Tinospora cordifolia* (guduchi),[141] and others.[4,131,135] Some of the active constituents include phenolics,[139] flavonoids,[142] alkaloids,[143] saponins and steroids[144] and many more.[135] Glycyrrhizin,[145] glycyrrhizic acid,[130] catechin and curcumin[146] are some of the important active principles in few medicinal plants (Licorice, turmeric) believed to be effective against SARS-CoV-2. They may inhibit SARS-CoV-2 spike glycoprotein and non-structural protein-15,[147] can target RNA-dependent RNA polymerase,[148] protease enzymes like $3CL^{pro}$,[149] Mpro[146,150] or angiotensin-converting enzyme 2 (ACE2),[146,150] inhibit viral entry and replication[136,142] or can modulate immune and inflammatory response.[130] Some herbs have shown suppressive effects on NLRP3, caspase-1, IL-1b and are likely having inhibitory effects on SARS-CoV-2 as well, however need exhaustive evaluation.[4] In combination, vitamin C, curcumin, and glycyrrhizic acid are proposed to regulate immune and inflammatory response against SARS-CoV-2.[130] Vitamins D, C, and E, trace minerals zinc and selenium, and omega-3 fatty acids can be helpful in treating COVID-19 as they have immune-boosting role.[151] Vitamin C being an antioxidant and immunomodulator has been found to reduce cytokine storm in COVID-19 patients.[100] Vitamin D deficiency affects immunity, predisposes to COVID-19 in diabetic patients, as it has antioxidant and immunomodulatory effects hence can have therapeutic role in such COVID-19 patients.[152] Thus alone or in combination, dietary or medicinal ingredients can prove beneficial as alternative therapy of COVID-19, modulating immune response against SARS-CoV-2 with immunomodulation being the prime mechanism along with potent antiviral effects.

Of recent immunomodulation by thymosin alpha-1 (TA1), a 28-amino acid peptide originally isolated from thymic tissue has found prospects in immunotherapy of COVID-19.[153] Thymosin alpha 1 modulates biological responses. It plays an important role in activating and regulating various cells of the immune system.[154] Hence has found applications in diseases with immune alterations and infectious diseases.[154] It has been evaluated in treatment of COVID-19 in clinical trials.[155] Ta1 has been administered SC at a dose of 1.6 mg in 1 mL of diluent daily for 1 week in COVID-19 patients along with standard care. It has reduced mortality of COVID-19 by restorating

normal lymphocyte counts and reversing exhausted T cells.[153] Thymosin 1 alpha may be used to improve the thymus function and T lymphocyte numbers in COVID19-infected individuals and the clinical outcome as noted in recent clinical trial.[156] ZADAXIN™ a thymosin alpha 1 (thymalfasin) based product has been approved for treatment of Hepatitis B.[157]

So numerous immunotherapeutics are being explored in COVID-19 therapy.[158–160] Currently, the immunotherpeutics being evaluated in COVID-19 therapy are still under clinical trials as detailed in Table 1 and none has been approved fully yet for treatment of COVID-19. However many trials are in final stages of evaluation and in coming times there are hopes for developing safe and effective immunotherapeutics against COVID-19.[158–160]

Conclusion and Future Prospects

The gap generated due to the lack of an efficient vaccine against SARS-CoV-2 can be bridged using antibody-based immunotherapeutics for inducing short-term immunity and using immunomodulators to boost immunity. However, vaccines are the permanent solution for resolving the threat caused by SARS-CoV-2. Antibody-based immunotherapeutic strategies such as convalescent plasma, monoclonal antibodies (MAbs), neutralizing antibodies (NAbs), and convalescent plasma therapy have potential applications against COVID-19. NK cells, T cell-based therapies, cytokines, TLRs are also showing potential applications to safeguard against COVID-19. T cell receptor or chimeric antigen receptor engineered T cells can be used as therapeutic drug or vaccine for managing the COVID-19 in future. A combinatorial approach of using both antibodies and immune cells can be more effective in eliminating the virus from the body or prevention of the infection. The interplay of antibodies and the immune cells through antibody-dependent cytotoxicity is a key for the viral clearance. While these novel immunotherapeutic approaches are explored, the potential aggravation of disease or enhancement of the infection or adverse events should be kept in mind. As the cytokine storm is observed in some COVID-19 patients, a similar phenomenon is observed in high dose T cell therapies. For some viruses, the antibodies are known to enhance infection by acting as Trojan horse by transporting the virus into the host cell through the FCR receptors to establish the infection. The immunomodulators and adjuvants are also required to achieve the optimal-desired effect of immunotherapy. These are needed to boost a weak immune response or to control an excessive pathological immune response. As the immunotherapy brought lasting remission and cure to cancer patients, it has the potential to bring a complete cure to COVID-19 patients or use it for pre-exposure/post-exposure prophylaxis to prevent the pandemic spread of viruses such as SARS CoV-2 in future.

Though adaptive immunity through vaccination can hold key for future protection but harnessing innate immunity can help in eliminating SARS-CoV-2 and ameliorate COVID-19 disease. Diverse immunomodulatory options are being investigated but no immunomodulatory product has been approved as safe and effective. Immunomodulators and immunotherapeutics that help in viral clearance or prevent hyperinflammation can aid

Table 1. Details of the clinical trials on various immunotherapeutics against COVID-19.

Mode of Immunotherapy	Stages of the clinical trials (CT Registration No)	Number of patients enrolled	Current status	Evaluation/Results	Specificity
Convalescent plasma	3 (NCT04372979)	80	Recruiting	Prevented secondary worsening and reduced the risk to be transferred to intensive care, length of stay and mortality,	Specific to COVID-19
	2/3 (NCT04388410)	410			
	½ (NCT04384497)	50		decreased duration of oxygen therapy, cleared viremia/SARS-CoV-2, decreased duration of symptoms, inflammatory mediators, increased antibody response to SARS-CoV-2	
	1 (NCT04353206)	50			
Monoclonal Ab	NCT04354766	10	Recruiting	Comparing the serological profiles and neutralizing efficiency of plasma to the neutralizing capacities of the monoclonal antibodies generated with immortalized B cells.	Specific to COVID-19
Immunoglobulin (IVIG)	4 (NCT04411667)	34	Not recruiting rest all recruiting	Clinical signs, no. of patients requiring mechanical ventilation, oxygen therapy and length of stay, mortality, organ status, immunological, biochemical, hematological profile and adverse reactions.	Specific to COVID-19
	3 (NCT04350580)	138			
	2/3 (NCT04261426)	80			
	2 (NCT04432324)	100			
	½ (NCT04521309)	50			
IFN-α	3 (NCT04320238)	2944	Recruiting	Onset of COVID-19, clinical signs, viral clearance, viral kinetics, immunological kinetics and adverse effects	Specific
	½ (NCT04379518)	44			
IFN-β	4 (NCT04350671)	40	Enrolling by invitation	Improvement in clinical signs, mortality, SpO2 improvement, incidence of new mechanical ventilation use, duration of hospitalization, and adverse events, safety and tolerability, progression to pneumonia, viral clearance, blood ad sputum biomarkers.	Specific
	4 (NCT04350684)	40	Recruiting		
	2 (NCT04385095)	820			
IFN-λ	2 (NCT04343976)	20	Enrolling by invitation	COVID PCR testing, symptomatic improvement, improved clinical outcomes, resolution of hypoxia, fever, rate of progression to requiring critical care, overall survival, time to discharge, and adverse events.	Specific
	2 (NCT04388709)	66	Not yet recruiting		
	2 (NCT04344600)	164	Recruiting		
NK cell	½ (NCT04344548)	10	Not yet recruiting	NK transfer Immunogenicity and adverse events	

(*Continued*)

Table 1. (Continued).

Mode of Immunotherapy	Stages of the clinical trials (CT Registration No)	Number of patients enrolled	Current status	Evaluation/Results	Specificity
T cell	½ (NCT04276896)	100	Recruiting	Clinical improvement, lung lesions, mortality, duration of mechanical ventilation and hospitalization, RT-PCR testing, inflammatory biomarkers, adverse events.	Specific
CAR NK cell	½ (NCT04324996)	90	Recruiting	Clinical response and side effects	Not specific
MSC	2/3 (NCT04366063)	60	Recruiting	Blood oxygen saturation, intensive care unit-free days, clinical symptoms, respiratory efficacy, biomarkers concentrations in plasma, hospital stay, CT scan, changes in viral load, changes of CD4+, CD8+ cells count and concentration of cytokines, C-reactive protein, mortality, adverse events assessment, safety and efficacy of the administration of allogeneic mesenchymal stem cells, duration of stay, mortality	Not specific
	½ (NCT04346368)	20	Not yet recruiting		
	½ (NCT04366323)	26	Recruiting		
	1 (NCT04276987)	24	Completed		
IL-6 blockade	4 (NCT04377750)	500	Recruiting	Survival, clinical status assessment, duration of hospitalization, no. of deaths, improvement of the respiratory function, resolution of fever, viral load on blood and sputum, plasma concentration of GM-CSF, plasma concentration of Il-6, plasma concentration of TNF-α, rate of progression of White Blood Cell (WBC) fraction	Specific
	2 (NCT04357808)	30	Active, not recruiting		
	2 (NCT04370834)	217	Suspended (pending evaluation of data from other trial)		
	1 (NCT04386239)	40	Not yet recruiting		
IL-1 blockade	2/3 (NCT04324021)	54	Recruiting	Time to mechanical ventilation, change in total score, oxygen saturation (SpO2), partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2), pH, carbon dioxide tension (pCO2), oxygen tension (pO2) in hemogasanalysis, potassium, sodium, chloride, lactic acid, hemoglobin, oxygen supplementation, ferritin, CT of chest, lactate dehydrogenase (LDH), D-dimers, hemato-biochemicals, immunological biomarkers, viral load, ventilator free-days, change of baseline total sequential organ failure assessment (SOFA) score, survival and time to hospital discharge	Specific
	2 (NCT04341584)	240	Not yet recruiting		
	2 (NCT04339712)	40	Recruiting		
IFN-γ blockade	2/3 (NCT04324021)	54	Recruiting	No. of patients not requiring invasive mechanical ventilation or Extracorporeal membrane oxygenation (ECMO), time to mechanical ventilation, Modified Early Warning system score, change in total score, oxygen saturation (SpO2), partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2), pH, carbon dioxide tension (pCO2), oxygen tension (pO2) in hemogasanalysis, potassium, sodium, chloride, lactic acid, hemoglobin, oxygen supplementation, ferritin, CT of chest, lactate dehydrogenase (LDH), D-dimers, hemato-biochemicals, immunological biomarkers, viral load, ventilator free-days, change of baseline total sequential organ failure assessment (SOFA) scoresurvival and time to hospital discharge	Specific
TNF blockade	2 (NCT04370236)	366	Recruiting	Proportion of participants with disease progression, all-cause mortality, who transfer to ICU level care, a new onset of neurologic disease, evidence of new CHF or new MI, new onset embolus or thrombus, develop a need for renal replacement therapy, an increase in the WHO Ordinal Scale of Clinical Improvement score, length of hospital stay and inflammation markers	Specific

in treating COVID-19 patients. Passive antibody therapy and use of interferon αβ and IL-6 receptor (IL-6 R) inhibitor has been suggested. Disease-modifying anti-rheumatic drugs (DMARDS) including hydroxychloroquine, glucocorticoids, leflunomide, tocilizumab, baricitinib, thalidomide etc. have also been proposed for immunomodulation purposes in COVID-19. Adalimumab (anti-TNF), eculizumab (anti-C5), sarilumab (anti-IL-6), ixekizumab (anti-17A), meplazumab (anti-CD147), camrelizumab (anti-PD-1), recombinant IL-2, CSA0001 (LL-37 antiviral peptide), CD24FC (fusion protein inhibiting TLR stimulation, activating Siglec signaling causing immunosuppression) and rhG-CSF are other immunomodulatory options. Fingolimod (trade name Gilenya, of Novartis Company) is a sphingosine-1-phosphate receptor regulator (FTY720) with immunomodulating activity and is most commonly used against multiple sclerosis.

Despite the considerable achievements in immunotherapeutics in treating COVID-19 patients and few being readily available while others showing prospects for future development and application however specificity, effectiveness, safety, side effects, availability, cost effectiveness, affordability, and long-term efficacy will be some of the prerequisites that need to be evaluated for future application to treat appropriately COVID-19 patients and prevent health hazards thereby minimizing human sufferings that have been inflicted due to COVID-19 pandemic.

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ORCID

Mohd. Iqbal Yatoo http://orcid.org/0000-0002-4501-7354
Ranjit Sah http://orcid.org/0000-0002-2695-8714
Ruchi Tiwari http://orcid.org/0000-0001-6897-3472
Muhammad Bilal http://orcid.org/0000-0001-5388-3183
Harapan Harapan http://orcid.org/0000-0001-7630-8413
Kuldeep Dhama http://orcid.org/0000-0001-7469-4752

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