International Journal of Pharmacy and Pharmaceutical Sciences

Print ISSN: 2656-0097 | Online ISSN: 0975-1491 Vol 14, Issue 11 2022

Review Article

COMPREHENSIVE THERAPEUTIC INTERVENTIONS AGAINST SARS-COV-2: A REVIEW AND PROSPECTIVE

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Received: 27 Aug 2022, Revised and Accepted: 24 Sep 2022

ABSTRACT

In December 2019, Wuhan City, Hubei Province, China, first reported pneumonia like symptoms with unknown aetiology caused by a novel coronavirus. The novel coronavirus was renamed as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by Coronaviridae Study Group of the International Committee on Taxonomy of Viruses and the disease was termed as Coronavirus Disease 2019 (COVID-19). As of 19 August, 2022, the infection has reached above 220 countries, areas or territories with a total of 591 683 619 confirmed cases and 6 443 306 deaths, as published by the World Health Organization (WHO). SARS-CoV-2 is strongly contagious as it has R_0, 2.2-2.6, in comparison to SARS-CoV (<1) and Middle East respiratory syndrome coronavirus (MERS-CoV) (1.4-2.5), respectively. SARS-CoV-2 might become less virulent than the SARS-CoV and MERS-CoV, with the currently analyzed mortality of COVID-19 is 3.4%. The original SARS-CoV-2 has undergone "virus evolution" with the occurrence of numerous variants such as Alpha, Beta, Gamma and Delta etc. Recently, the circulating variant of concern is Omicron subvariants. Currently, real-time reverse transcription–polymerase chain reaction-based detection of the viral genome (RNA) is the gold standard for diagnosis of SARS-CoV-2 infection. At present, Remdesivir (RDV) and Baricitinib drugs as well as vaccines Pfizer-BioNTech and Moderna have been approved for the treatment of COVID-19 by Food and Drug Administration (FDA). In this review, we summarized the existing state of knowledge on approved antiviral therapy, combination therapy, blood-derived therapeutics and immunomodulators to treat COVID-19 pandemic.

Keywords: COVID-19, SARS-CoV-2, Coronavirus, FDA, Convalescent plasma, Virus evolution

DOI: https://dx.doi.org/10.22159/ijpps.2022v14i11.46171. Journal homepage: https://innovareacademics.in/journals/index.php/ijpps.

INTRODUCTION

The novel coronavirus, SARS-CoV-2 belonged to beta-coronavirus class, family Coronaviridae and order Nidovirales [1, 2]. SARS-CoV-2 has been hypothesized to originate from bat CoV, RaTG13 (96% whole genome level). Pangolin-CoV was hypothesized to be the second closest relative of SARS-CoV-2 (91.02% whole genome level) [3, 4]. Poor proofreading capability of the viral RNA polymerase and homologous recombination between CoVs might be the probable reasons of fast mutational frequency that might contribute to "cross-species" transmission [5, 6]. COVID 19 genome consisted of single-stranded RNA composed of about 30 kb nucleotides, 5'-untranslated region (UTR), a replicase complex (orf1ab) encoding non-structural proteins (nsps), a spike protein (S) gene, envelope protein (E) gene, a membrane protein (M) gene, a nucleocapsid protein (N) gene, 3'-UTR, and several unidentified non-structural open reading frames [7, 8]. The global trend of COVID-19 confirmed cases and associated deaths from January 04, 2021 to August 22, 2022 have been reported [9] as shown in fig. 1. The highest percentage of COVID-19 confirmed cases as per WHO region was reported in Europe while the least has been reported in Africa [10] given in fig. 2.

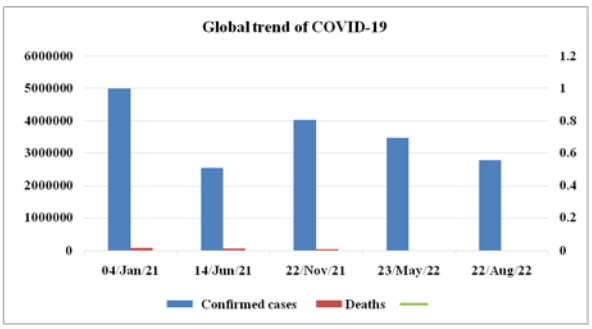

Fig. 1: Global trend of COVID-19 cases and associated deaths

Whole genome sequencing of WH-Human 1 coronavirus (WHCV) was performed [11]. It was reported that enhancement of the nuclear localization signals in the nucleocapsid protein and well-defined inserts in the spike glycoprotein that appeared to be linked with a high case fatality rate of CoVs as well as the zoonotic transmission to humans were the main genomic features that distinguished SARS-CoV-2 from less pathogenic coronaviruses [12]. Human angiotensin-converting enzyme 2 (hACE2) has been declared to be the functional receptor of SARS-CoV-2 [13].

COVID-19 incubation period was 14 d, with a median time of 4-5 d from exposure to onset of symptoms [14-16]. The symptoms of COVID-19 reported were: fever, cough, fatigue, shortness of breath or difficulty breathing, muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting and diarrhoea [17, 18-22]. The clinical manifestations of COVID-19 ranged from asymptomatic to severe pneumonia with severe acute respiratory distress syndrome (ARDS), septic shock, and ultimately multiple organ dysfunction syndrome (MODS) [23].

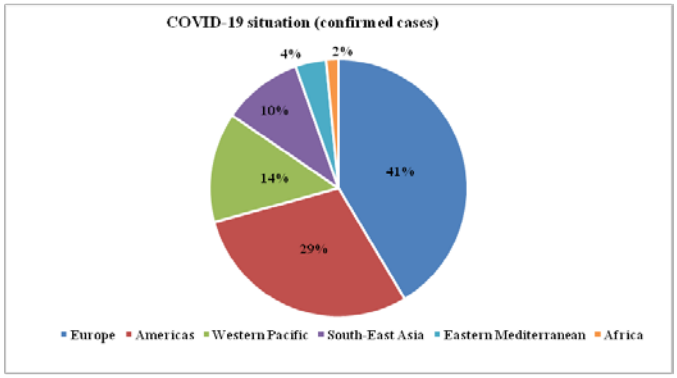

Fig. 2: Situation by WHO region showing confirmed cases of COVID-19 till August 24, 2022

The primary mode of infection was human-to-human transmission which occurred via respiratory secretions [24], which is why it is necessary to keep a distance of more than two meters from a sick person. Other modes included infected inanimate objects and it has been shown that the virus remains alive on surfaces for possibly up to 9 d [25, 26]. Recently, blood group A was correlated with an increased risk, whereas blood group O was associated with a decreased risk, thus indicating that the ABO blood type is a biomarker for differential susceptibility of COVID-19 [27]. In COVID-19 Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is activated by Type I inteferons (IFNs), which lead to an antiviral gene expression program [28]. The immunopathology of the lung might be the consequence of the "cytokine storms" which lead to pneumonitis, ARDS, respiratory failure, shock, multiple organ failure and potentially death. Systemic and controlled COVID-19 drug development processes are essential approaches to combat the current COVID-19 pandemic.

Source of information

For obtaining recent quantitative, factual data about SARS-CoV-2 effects on the worldwide population (cases and deaths), diverse organizations' such as WHO, FDA etc. were explored in depth. In addition, various electronic bibliographic databases were thoroughly searched. For formatting and presentation of information, relevant review articles were referred. Key text words, such as "virus evolution", "therapeutic" published till 2022 were utilized in MEDLINE. Furthermore, contemporary research articles of published studies with appropriate information on the SARS-CoV-2 pathogenesis and drug therapies targeted against SARS-CoV-2 were consulted. For filling in with the fresh knowledge, relevant books, conference proceedings and public health organization survey reports were collated based on the wider objective of the review. This was achieved by looking for databases, including Web of Science, SCOPUS, EMBASE, Pubmed, Publon, PMC, Swiss rot, Google searches. From this specified methodology, findings were identified and summarized in this review. Furthermore, additional relevant references were incorporated through searching the references cited by the studies performed on the present topic.

Potential therapeutics under evaluation for the treatment of COVID-19 infection

RDV

RDV is a broad-spectrum antiviral monophosphoramidate prodrug of adenosine analogue with potent *in vitro* antiviral activity against a heterogenous panel of RNA viruses [29-32]. Different studies were undertaken out using RDV treatment in COVID-19 patients which resulted in clinical improvement [33-37]. RDV is the primary therapeutic antiviral treatment with proven potent efficacy against COVID-19 in an animal study which reported significant clinical benefit, a reduction in pulmonary infiltrates, and a reduction in pulmonary pathology. It further suggested that RDV treatment in COVID-19 patients should be initiated as early during infection to prevent advancement to severe pneumonia and to achieve the maximum clinical benefit because another study reported that the efficacy of direct-acting antivirals (DAAs) against acute viral infections typically decreased with delay in initiation of treatment. Adaptive COVID-19 Treatment Trial (ACTT), sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH) in COVID-19 hospitalized adults reported that patients who received IV RDV had a shorter time to recovery than those who received placebo and survival benefit, with a 14 d mortality rate of 7.1 % for the RDV treated group versus 11.9 % for the placebo group; although, the difference in mortality was not statistically significant. RDV treatment along with concomitant use of lopinavir-ritonavir, IFNs, and corticosteroids in adult COVID-19 patients and reported that RDV was not associated with a difference in time to clinical improvement, 28 d mortality, or rate of viral clearance between the RDV and the placebo-treated patients [38].

Chloroquine (CQ)

CQ is a 9-aminoquinoline that was synthesized in 1934 as a potent substitute for natural quinine used against malaria and was widely used to treat various human diseases [39-42]. Antiviral efficacy of CQ against COVID-19 might be evident from its past antiviral inhibitor roles against SARS-CoV, HCoV-OC43, influenza A H5N1, HCoV-229E, and EBOV in various cell line [43-48]. CQ was probably the first antiviral drug utilized in China and abroad as the front-line treatment against COVID-19 infections [49]. The first human trial conducted with chloroquine against COVID-19 reported that CQ reduced symptom duration, increased pneumonia, promoted the radiological improvement and virus-negative seroconversion without any severe adverse effects [50]. Various studies demonstrated no antiviral benefits associated with CQ in COVID-19 [51, 52].

Hydroxychloroquine (HCQ)

HCQ, an analogue of CQ, was used for the treatment of autoimmune diseases, such as systemic lupus erythematous (SLE) and rheumatoid arthritis [53]. HCQ differed from CQ by the presence of a hydroxyl group at the end of the side chain: the N-ethyl substituent is β-hydroxylated-1 [54] which conferred it with lesser risk of retinal toxicity as compared to CQ [55]. HCQ offered an immense advantage of being employed in high doses for long periods with very good tolerance and had a lower potential for drug-drug interactions than CQ [56]. A study suggested that incubation time might influence the antiviral activity of the drug because it is possible that a longer incubation time might provide more time for the drug to accumulate in higher intracellular concentrations and ultimately exhibit a potent antiviral effect [57]. Another study reported that clinical outcomes with HCQ in COVID-19 patients were overall survival, survival without ARDS, weaning from oxygen, and discharge from the hospital [58]. Diverse studies reported no clinical benefit associated with HCQ treatment against SARS-CoV-2 [59-61].

Combination therapy

Hydroxychloroquine plus azithromycin (HCQ+AZM)

Azithromycin (AZM) is utilized to treat a variety of bacterial and viral infections [62-64]. Combination treatment of AZM with HCQ has been involved in mixed clinical outcomes in COVID-19 [65-67].

Few studies have reported no clinical benefits with combination treatment of AZM with HCQ in COVID-19 [68-70].

Lopinavir/Ritonavir (LPV/RTV)

LPV, a highly potent, selective [71] and peptidomimetic [72] inhibitor of HIV type 1 aspartate protease inhibitor, usually combined with RTV to elevate its plasma half-life through the suspension of CYP450 has been reported to exhibit *in vitro* anti-MERS-CoV and anti SARS-CoV activity [73-75]. Combination therapy of LPV/RTV with IFN-β against MERS-CoV reported clinical benefits [76]. Various studies suggested that the administration of LPV/RTV regimen during early COVID-19 infection was effective in alleviating the viral load and improving clinical benefits in patients with mild to moderate disease [77, 78]. Numerous studies reported no clinical benefit associated with LPV/RTV treatment against SARS-CoV-2 infection [79-81].

Darunavir/Cobicistat (DRV/c)

Prophylactic DRV/c approved for the treatment of HIV-1 is a protease inhibitor. DRV acted as an inhibitor of the dimerization and of the catalytic activity of the HIV-1 protease, whereas c inhibited CYP450 that increased DRV plasma concentrations [82] Of note, DRV should not be administered without a boosting agent (RTV or c) as previous studies reported that DRV alone resulted in subtherapeutic drug levels and was linked with a higher rate of adverse events [83]. Clinical data on the use of treatment of (DRV/c) on COVID-19 is limited.

Blood derived therapeutics

Convalescent plasma (CP)

CP therapy, immunotherapy to achieve immediate short-term immunization against infectious agents where the humoral antibody (Ab) retrieved from the recovered patient was administered to a susceptible patient used to neutralise the pathogen and eventually lead to its elimination from the blood circulation [84-86]. Treatment with CP dates back to the end of the 19th century, in treatment of diphtheria and tetanus patients [87] and over the past decades, CP transfusion has proved its specificity and effectiveness as a potential treatment in patients with MERS-CoV [88], H1N15 [89], SARS-CoV [90-92] and cancer therapy which could help ameliorate survival rates in patients whose condition deteriorated even with conventional treatment. Previous studies of SARS and severe influenza recommended transfusion of CP as early as possible because the production of endogenous IgM and IgG antibodies summitted at 2 w and 4 w after infection, respectively [93]. To employ convalescent serum administration for COVID-19 the following six conditions must be met: (i) availability of donors (ii) blood banking facilities (iii) availability of assays to detect virus in serum and to estimate viral neutralization; (iv) virology lab facilities (v) randomized clinical trials (vi) regulatory compliance, comprising institutional review board approval, which might vary depending on location [94].

Different studies reported positive clinical outcomes using CP treatment in COVID-19 patients with few or no adverse events [95-99]. Neutralizing antibodies responses to SARS-CoV-2 in COVID-19 patients and convalescent patients was analyzed and reported that COVID-19 patients were seropositivity to SARS-CoV-2 during early stages, an evident neutralizing antibody response was observed in convalescent patients, and reduced antibody levels in asymptomatic or mild patients than moderate or severe patients which were consistent with results from previous studies. Another recent Chinese descriptive study in Wuhan, conducted in 6 laboratories, confirmed COVID-19 patients who received the transfusion of ABO-compatible CP and the results showed alleviation of symptoms, ameliorating radiologic abnormalities and laboratory tests and no obvious adverse effects were observed. Of note, this study speculated that anti-SARS-CoV-2 IgM and IgG directly neutralized the virus, and the anti-inflammatory contents might prevent cytokine stores recent study reported no significant clinical benefit associated with CP Therapy in severe COVID-19 patients [100].

Non-SARS-CoV-2-specific intravenous immune globulin

Liquid preparations of human immunoglobulin (pH 4) contained IgG antibody against a broad spectrum of antiviral, bacterial or other pathogens which could rapidly elevate the IgG level in the blood, directly neutralized exogenous antigens, and regulated various immune functions [101]. IVIG has been extensively utilized in the treatment of serious bacterial and viral infections and sepsis with positive and negative clinical outcomes [102-105]. A study of IVIG treatment in COVID-19 patients reported decreased 28 d mortality, minimized inflammatory response, ameliorated organ functions (all $p<0.05$) and 60 d mortality decreased significantly by using IVIG at an early stage (admission ≤7 d) and with high dose (>15 g/d). Another study reported IVIG was associated with significantly reduced hypoxia, duration of hospital stays and need of mechanical ventilation requirement in COVID-19 patients [106].

Mesenchymal stem cell (MSC) therapy

MSCs are multipotent adult stem cells with self-renewable property i.e.; they are divided and differentiated into multiple types of tissues. MSC therapy was superior to other treatments because of: (i) easily accessed and isolated from different tissues (ii) it simply expanded to clinical volume in a suitable period of time (iii) could be stored for repetitive clinical usage; (iv) clinical trials of MSCs till date hasn't shown adverse effects to allogeneic MSC; (v) safety and effectiveness of MSCs in several clinical trials [107]. Leng and colleagues demonstrated the safety and efficacy of IV MSC transplantation in COVID-19 patients and reported improving pulmonary status, reduced C-reactive protein (CRP) levels, and lowered inflammatory cytokines whilst IL-10 escalated and hyperactivity cytokine secreting immune cells dissipated after a few days [108]. Treatment with human umbilical cord mesenchymal stem cells (hUCMSC) in a critically ill COVID-19 patient resulted in the return of all measured parameters to normal levels and suggested that hUCMSC could be an ideal therapeutic option alone or in parallel with other immune modulators for acute COVID-19 patients [109].

Immunomodulators

Corticosteroids

Corticosteroids are systemic anti-inflammatory and classical immunosuppressive drugs which terminated or delayed the progression of pneumonia and have been shown to be effective against the treatment of ARDS [110-112]. Corticosteroids were widely used during past CoV outbreaks [113-115], in addition to other therapeutics, which reported no significant effect on clinical outcomes but increased mortality and requirement of mechanical ventilation. It was reported that it was difficult to make a clear recommendation to corticosteroid treatment of SARS patients, particularly because the drug is immunosuppressive and might delay viral clearance if administered before viral replication is controlled. The RECOVERY (Randomised Evaluation of COVid-19 therapy) trial reported that low-cost dexamethasone at a dosage of 6 mg once daily for up to 10 d alleviated 28 d mortality in COVID-19 hospitalized patients with severe respiratory complications [116]. Different studies reported that early, low-dose and short-term application of intravenous methylprednisolone in severe COVID-19 patients was associated with a rapid improvement of clinical symptoms and absorption of lung focus with little or no serious complications [117-119]. A retrospective observational study of corticosteroids on outcomes of COVID-19 patients revealed that treatment within 72 h after the first signs could reasonably reduce the risk of disease exacerbation in non-severe patients which were consistent for other virus-induced diseases [120]. Several studies reported no effective clinical outcomes associated with corticosteroid treatment in COVID-19 patients but an increased risk of mortality and secondary infections [121-123].

IFNs

IFNs are cellular surfaces' receptor binding proteins which initiated JAK-STAT signalling cascades, with transcriptional regulation of genes and effective against certain viruses like hepatitis B virus and HCV [124]. Several MERS-CoV studies were carried out using different combinations of IFNα and IFNβ with ribavirin some of which reported an association or no association with reduction in mortality [125-127]. Varied types of IFNs belonging to the three classes (α, β and γ) reported effective anti-SARS-CoV activities [128,

129]. A study was conducted in severe COVID-19 patients with subcutaneous administration of IFNβ-1a which reported escalating discharge rate on day 14 and alleviated 28 d mortality with improved survival during the early course of administration [130]. Treatment with nebulized IFN-α2b in adults hospitalized confirmed COVID-19 patients reported shortened duration of viral shedding and synchronously decreased the markers of acute inflammation such as CRP and IL-6 [131]. Triple combination treatment with INF β-1b, LPV/RTV, and ribavirin in COVID-19 patients reported that therapy was safe and superior to LPV/RTV alone in decreasing symptoms and reducing the duration of viral shedding and hospital stay [132]. An experimental open-label study suggested that recombinant human interferon alpha (rhIFN-α) nasal drops to be a promising agent for protecting COVID-19 susceptible healthy people [133]. Combination treatment of IFN-α2b and IFN-γ with the standard of care in confirmed COVID-19 patients was associated with rapid viral elimination, reduced CRP levels and improved clinical parameters [134].

Interlukin-1 (IL-1)-Anakinra

Anakinra, a 17-kD recombinant, non-glycosylated antagonist (IL-1Ra) that only differed from the known IL-1Ra due to the presence of an extra methionine residue at the N-terminal end [135, 136]. Continuous intravenous anakinra infusion in severely ill adult patients with macrophage activation syndrome (MAS) resulted in rapid serologic and subsequent clinical improvement [137]. Various studies reported positive clinical outcomes associated with anakinra treatment in COVID-19 patients with the occurrence of few adverse events [138-140].

IL-6 Inhibitors (Tocilizumab, Sarilumab, Siltuximab)

Tocilizumab (TCZ)

TCZ is a recombinant humanized anti-interleukin-6 receptor (IL-6R). TCZ treatment in moderate to severe COVID-19 patients was found to be effective and resulted in improved survival and reduced the risk of mortality [141-143].

Siltuximab

Siltuximab is a human-mouse chimeric IL-6R monoclonal antibody [144]. IV siltuximab treatment in COVID-19 patients with pneumonia requiring ventilatory support showed reduced serum CRP levels, and improved clinical condition with increased deterioration in few patients [145]. However, clinical data on the use of siltuximab in COVID-19 treatment is limited.

Sarilumab

Sarilumab is the recombinant human monoclonal antibody IL-6 receptor antagonist approved in various countries to treat RA in adults. Phase 2/3 adaptive-designed trial of Sarilumab in severe or critical COVID-19 patients reported rapidly reduced CRP levels as the primary endpoint and "negative trends" for most outcomes in severe patients [146]. Clinical data on the use of Sarilumab in COVID-19 treatment is limited.

Bruton's tyrosine kinase inhibitors (BTK) inhibitors

Acalabrutinib

Acalabrutinib, a highly specific covalent BTK inhibitor authorized in the U. S for the treatment of lymphoid malignancies [147]. Roschewski and colleagues conducted an off-label study using acalabrutinib in severe COVID-19 patients and reported improving oxygenation and reduced levels of inflammatory markers (CRP and IL-6) with no discerning toxicity [148]. However, clinical data on the use of acalabrutinib in COVID-19 infection is limited.

Ibrutinib

Ibrutinib is a highly potent and covalent BTK inhibitor. A study conducted by American Society of Hematology (ASH) suggested that ibrutinib might provide protection against pulmonary injury in COVID-19 patients [149]. However, clinical data on the use of ibrutinib in COVID-19 infection is limited.

JAK inhibitors

Baricitinib

Baricitinib is an oral, reversible, selective and potent JAK inhibitor approved by the FDA to treat rheumatoid arthritis and could improve the chronic inflammation seen in interferonopathies [150-153]. It was reported that therapeutic dosage of baricitinib with either 2 mg or 4 mg once daily was adequate to reach the plasma level of inhibition. In addition, he suggested that this drug could be a potential treatment for COVID-19 acute respiratory disease [154]. Baricitinib therapy in COVID-19 patients reported significantly improved clinical characteristics and none of the patients required ICU support, and the majority of the patients were discharged [155].

Ruxolitinib

Ruxolitinib is (JAK)1/2 inhibitor that has shown JAK-STAT inhibition in COVID-19. Ruxolitinib treatment in COVID-19 patients reported escalating clinical improvement, improved chest CT images and rapid recovery from lymphopenia and demonstrated the efficacy and safety [156]. Another study of ruxolitinib treatment in COVID-19 patients with severe systemic hyperinflammation reported sustaining clinical improvement [157].

Comprehensive, detailed information about COVID-19 treatment options is given in table 1. Recently, RDV has been approved by FDA in hospitalized adults and pediatric patients (aged ≥12 y and weighing ≥40 kg [158]. BTK and JAK inhibitors demonstrated potential anti-SARS-CoV-2 activity but data is limited. Some of them are showing encouraging results with less or no side effects but still need to investigate in details and in spite of therapeutic interventions. Other strategies like blood-derived products, immuno-modulators etc. are also in different stages of clinical trials [159-163].

Table 1: List of therapeutic interventions for COVID-19 treatment

S. No.	Drug	Route of administration	Mechanism of action in COVID-19	Adverse effects	Reference
Antiviral therapy					
1.	RDV	IV[a]	• RNA[b]polymerase inhibitor with *in vitro* and *in vivo* anti SARS-CoV[c]-2 activity at low µm concentration (EC_{50}[d] = 0.77 µM; CC_{50}>100 µM; SI>129.87).	• Pyrexia • GI[e] symptoms • Multiple organ-dysfunction syndrome • Acute kidney injury • Hypotension • Mortality	[35, 37, 38]
2	CQ	Oral	• Increases endosomal pH levels and suspends virus endosome fusion. • *In vitro* (EC_{50}=5.47 µM) and *in vivo* inhibitory activity against SARS-CoV-2 at low µm concentration (EC_{50} = 1.13 µM).	• Cough • Shortness of breath • GI symptoms • Death	[35, 52, 57, 164]
3.	HCQ	Oral	• Similar to the mechanism of action of CQ[f]. • Potent anti-SARS-CoV-2 activity *in vitro*	• GI symptoms • Cardiac arrhythmia	[57, 58, 60, 165]

S. No.	Drug	Route of administration	Mechanism of action in COVID-19	Adverse effects	Reference
			(EC_{50}=0.72 μM).	• Chronic kidney failure • Diabetes • Death	
Combination therapy					
4.	HCQ+AZM	Oral	• Induction of IFN[g]-stimulated genes, attenuating viral replication. • Immunomodulatory effects • Anti-Inflammatory effects	• GI symptoms • Cardiac arrest • Diabetes mellitus • Chronic kidney disease • Death	[66, 166, 167, 168]
5	HIV Protease Inhibitors (LPV/RTV and DRV/c)	Oral	• Possible inhibitory activity on SARS-CoV-2 proteases (3CLpro[h] and (PLpro[i]) required for replication. • *In vitro* SARS-CoV-2 effect of Lopinavir (EC_{50} at 26.1 μM) in Vero E6 cells.	• Pyrexia • Cough • GI symptoms • Respiratory failure/ARDS[j] • Biochemical hepatitis • Mortality	[79, 81, 132, 169, 170]
Blood derived therapeutics					
6.	CP	IV	• Passive Antibody therapy.	• TACO[k] • TRALI[l] • Shortness of breath • Respiratory failure • Cardiac events • Death	[95, 171]
7.	Non-SARSCoV-2 Specific IVIG[m]	IV	• Direct neutralization of exogenous antigens and regulation of multiple immune functions by human immunoglobulin (pH4) containing IgG antibody.	• Bacterial super infections • Thrombocytopenia • Lymphocytopenia • Mortality	[101-103, 106]
8.	MSCs	IV	• Robust immunomodulatory and anti-inflammatory activity. • Promotion of endogenous repair and improvement of the pulmonary microenvironment and function.	• No adverse effect observed in COVID-19[n].	[108]
Immunomodulators Corticosteroids					
9.	Dexamethasone	Oral IV	• Potent anti-inflammatory and immunosuppressive effects. • Detrimental effect on angiotensin II which played a key role in the pathophysiology of SARS-CoV-2.	• Cardiac arrhythmia • Renal replacement • Hyperglycaemia • Barotrauma • Mortality	[21, 123, 172-177]
10.	Methylprednisolone	IV		• Hyperglycaemia • ARDS • Mortality	
11.	Adjuvant corticosteroid therapy (Hydrocortisone)	IV		• Secondary infections • Multiple organ dysfunction • Mortality	
IFNs (alpha, beta and gamma)					
12	IFN-alpha	Inhalation Intramuscular (IFN-α2b)	• The EC_{50} of IFN-α in SARS-CoV-2 treatment in Vero cells is 1.35 IU/ml. • Reduction of the infection rate of SARS-CoV-2 by IFNα2b spray. • Down regulation of the inflammatory biomarker IL-6 °by IFN-α2b.	• Pyrexia • Dry Cough • GI symptoms • Worsening of the respiratory system	[131] [178] [179]
13.	IFN-β	Subcutaneous injection (IFN-β1b) IV injection (IFN-β1a)	• The EC_{50} of IFN-β in SAR-CoV-2 treatment in Vero cells is 0.76 IU/ml. • Upregulation of CD73[p], prevention of vascular leakage and inhibition of leukocyte recruitment by IFN-β-1a.	• Pyrexia • GI symptoms • Injection site reactions • Renal impairment • Hepatic impairment • Mortality	[130] [178] [180] [181] [182]
14.	IFN-γ	Subcutaneous	• Immunomodulatory effects • Anti-inflammatory effects • Restricts ACE2[q]expression.	• GI symptoms • Worsening of respiratory symptoms • Headache	[134] [183]
IL-1					
15.	Anakinra	IV Subcutaneous	• Blocks the binding of IL-1α[r] and IL-1β[s] to IL-1R[t] by mirroring the mode of action of its endogenous counterpart. • Neutralization of SARS-CoV-2 hyperinflammatory state.	• Septic shock • Bacteremia • Acute respiratory failure • Multiorgan failure	[136] [137] [184]

S. No.	Drug	Route of administration	Mechanism of action in COVID-19	Adverse effects	Reference
IL-6					
16.	TCZ	IV Subcutaneous	• Humanized anti IL-6R[u] antibody which competitively inhibits both the soluble and membrane-bound forms of the IL-6R. • Suppression of cytokine storm in critically ill COVID-19 patients.	• Infections • Liver failure • Injection site reactions. • Renal replacement • Death	[141] [142] [143] [185]
17.	Sarilumab	Intravenous	• IL-6R receptor antibody which inhibits IL-6-mediated signalling. • Reduction of the hyperactive inflammatory immune response associated with COVID-19.	• Hypotension • Multiple organ dysfunction • Mortality	[146] [186]
18.	Siltuximab	Intravenous	• Chimeric antibody against IL-6R that binds to and blocks the effect of IL-6.	• Death • Cerebrovascular event	[145]
Kinase inhibitors: BTK inhibitors and JAK inhibitors					
19.	Acalabrutinib	Oral	• Macrophage signaling and activation in COVID-19. • Inhibition of the BTK[v] induced pathological hyperinflammatory response in severe COVID-19.	• Pyrexia • Headache • Cardiac arrhythmias • Opportunistic infections • Upper respiratory tract infections	[148]
20	Ibrutinib	Oral	• Protects against pulmonary injury in COVID-19.	• Serious bleeding • Proarrhythmic • Effect. • Dyspnea • Hypoxia	[149]
21	Baricitinib	Oral	• JAK-STAT[w]signalling inhibitor. • Interferes with receptor-mediated endocytosis and clathrin-mediated endocytosis.	• Upper respiratory tract infections.	[18, 151, 187]
22	Ruxolitinib	Oral	• Targeted inhibition of cytokine signaling in COVID-19. • Reduction of systemic inflammation in COVID-19.	• GI symptoms • Hematological events • Headache • Liver dysfunction	[156] [157]

[a]Intravenous; [b]Ribonucleic acid; [c]Severe acute respiratory syndrome; [d]Half-maximal effective concentration; [e]Gastrointestinal; [f]Chloroquine; [g]Interferon; [h]3-chymotrypsin-like protease; [i]Papain-like protease; [j]Acute respiratory distress syndrome; [l]Transfusion-related acute lung injury; [m]Intravenous immunoglobulin; [n]Coronavirus disease 2019; [o]Interlukin-6; [p]Cluster of differentiation 73; [q]Angiotensin-converting enzyme 2; [r]Interleukin-1 alpha; [s]Interlukin-1 beta; [t]Interleukin-1 receptor; [u]Interlukin-6 receptor; [v]Bruton's tyrosine kinase inhibitor; [w]Janus kinase inhibitor-signal transducer and activator of transcription protein.

CONCLUSION

RDV has shown to be the most promising agent having potential anti-SARS-CoV-2 activity. Blood-derived therapeutics such as CP and IVIG demonstrated mixed clinical outcomes against SARS-CoV-2 with possible side effects. MSCs emerged as a safe and effective treatment of COVID-19 because of its increased proliferation rate, lowered invasive procedure, free from ethical issue and potential clinical benefits with no mortality in COVID-19 disease. Gene expression profiling study of transplanted MSCs showed that MSCs are ACE2- or TMPRSS2- indicating that MSCs are free from SARS-CoV-2 infection. Potent candidates repurposed could save time and cost, especially when vaccine is not available commercially. There is a requirement to study future COVID-19 variants, including their geographical spread, genetic changes and phenotypic characteristics to design effective vaccines against them. There is a need to increase the availability of diagnostic tests, medical devices, personal protective equipment kit and therapeutics for an effective COVID-19 response. Social distancing and caution are the magical formulas nowadays.

ACKNOWLEDGEMENT

We thank the anonymous referees for their useful suggestions.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

Nilanjana Prasad and Debanjana Prasad were responsible for the conception, experiments, and writing and revising the manuscript.

CONFLICT OF INTERESTS

Declared none

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