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Annals of Clinical and Biomedical Research 2021; volume 2:118

Mechanisms of action and adverse effects of the major therapeutic agents in trial for COVID-19 therapeutics: Review of literature

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Abstract

The race to find an effective cure for COVID-19 is on. Most of the candidate drugs in various clinical trials are being re-purposed but none has been approved as at date. It is pertinent for the bedside physicians to understand the mechanisms of action of these agents and their peculiar adverse effects so they are properly guided on the risk/benefit of the drugs they choose in managing COVID-19 patients. Clinicaltrials.gov, the international clinical trials platform of the WHO, the EU clinical trials register and the Cochrane Central Register of Controlled Trials were searched for registered clinical trials. Studies in therapeutic trials were considered eligible for the work. Frequency table was made for the most common trialled drugs and the mechanisms of actions and adverse effects of the selected drugs were reviewed. Ten studies were selected for review in a descending order of their frequency in different therapeutic trials and these are ritonavir, lopinavir, chloroquine/hydroxychloroquine, interferon, remdesvir, favipravir, umifenovir, darunavir, tocilizumab and methylprednisolone. The bedside physicians need to understand the mechanisms of action of these agents and their peculiar adverse effects for proper guidance on the risk/benefit of the drugs they choose in managing COVID-19 patients.

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Key words: COVID-19, therapeutics, clinical trials, repurposing, mechanisms of action, adverse effects.

Contributions: We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. EDO, CCO and OBE conceptualised and designed the work. EDO, CCO, OBE, CCM drafted the manuscript. EE and SG critically reviewed the draft manuscript for intellectual content. All the co-authors read and approved the final draft for submission.

Conflict of interest: The authors declare no conflict of interest.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate: Not applicable.

Informed consent: Not applicable.

Received for publication: 3 November 2020.
Revision received: 14 May 2021.
Accepted for publication: 14 May 2021.

Licensee PAGEPress, Italy
Annals of Clinical and Biomedical Research 2021; 2:118
doi:10.4081/acbr.2021.118

Introduction

Coronavirus disease 2019 (COVID-19), an infectious viral disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan in the Hubei province of China in December 2019.[1] It was declared a public health emergency of international concern and subsequently a global pandemic by World Health Organisation on 20th January 2020 and 11th March 2020 respectively.[2] As at 17th May 2020, there were about 4.5 million confirmed cases of COVID-19 and well over 300 000 deaths resulting from the pandemic globally.[3]

Most of the cases of COVID-19 (about 80%) are asymptomatic.[4] In the initial symptomatic phase of the disease, there could be flu-like clinical features like sore throat, dry cough, rhinorrhea, fever and fatigue. Myalgia, shortness of breath, haemoptysis, chest pain, diarrhea, nausea and vomiting, headache and confusion may set in subsequently. In the later phase, complications like Acute Respiratory Distress Syndrome (ARDS), pneumonia, arrhythmia and septic shock may set in.[5-8] It has also been observed that the symptoms are usually more severe in elderly patients with co-morbidities, in patients with allergic conditions like asthma, and patients with Chronic Obstructive Pulmonary Disease (COPD).[9]

As at date, neither drug nor vaccine has been approved for the treatment or prevention of this dreaded pandemic that has plunged the entire world into confusion and fear as well as socio-economic straits. However, a combination of oxygen therapy, mechanical ventilation, drugs like antivirals, antibiotics and other supportive therapies appear to give promising clinical outcomes in the management of COVID-19 patients.[8] These therapeutic agents are being used on "off-label" basis as they have not been approved for

use in COVID-19 patients. This "off-label" use is a way of drug repurposing (drug repositioning) in the bid to find fast-tracked remedy for the disease. Drug repurposing can be said to be the process of identifying and developing new uses for existing drugs.[10]

A recent study shows that as at 20th March 2020, about 344 interventional studies had been registered on clinical trials registries including ClinicalTrials.gov, WHO ICTRP, EU Clinical Trials Register, and Cochrane Central Register of Controlled Trials.[11] Also, WHO had on 18th March 2020 launched a clinical trial called SOLIDARITY to trial the four most promising drug candidates for COVID-19 treatment, namely: chloroquine/hydroxychloroquine, remdesvir, lopinavir/ritonavir and lopinavir/ritonavir/interferon beta-1a. This mega clinical trial is involving participants across over 90 countries.[12] Also, as at 14th April 2020, over 600 clinical trials on this subject matter had been registered with the WHO with about 133 of them being for therapeutic purposes.[12] Putting the therapeutic drug candidates together, they fall into about four major therapeutic groups: antivirals, antimalarials, immunosuppressants/immunomodulators and antibiotics. The antiviral candidates include remdesvir, favipiravir, lopinavir/ritonavir, ostelmavir, ganciclovir, peniclovir, umifenovir, triazavirin, baloxavir marboxil, danoprevir/ritonavir, azvudine, sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, darunavir/cobicistat, emtricitabine/tenofovir and ribavarin. The antibiotics include azithromycin, pirfenidone, carimycin and teicoplanin. The antimalarials are the chloroquine/hydroxychloroquine whereas the immunosuppressants/immunomodulators include glucocorticoids (corticosteroids, methylprednisolone, dexamethasone), anticytokines (tocilizumab, adalimumab, eculizumab, sarilumab, ixekizumab) pegylated interferon with ribavarin, lopinavir/ritonavir/interferon beta-1a.[11,12] This list is not exhaustive but enough to show that the race to find effective therapeutics for COVID-19 is certainly on and hopefully, some of these drug candidates will make it through the clinical trials and get formal approval.

Objectives

i) To review the mechanisms of action of the major drugs in clinical trials for COVID-19 therapeutics and ii) To highlight some of major adverse effects of these drugs to properly guide the moment-by-moment decision making of the front-line physicians.

Materials and Methods

We identified records of trials from online registries including Clinicaltrials.gov, the International clinical trials platform of the WHO, the EU clinical trials register and the Cochrane Central Register of Controlled Trials. We collated all registered trials and identified interventional studies focusing on therapeutic strategies. This identified 1835 studies. After removing duplicates, we had 915 studies from where we selected 490 that focused on therapeutic interventions having further removed studies on preventative interventions and vaccine trials. Another 150 studies were removed which was based on Chinese traditional and complementary interventions, leaving a total of 228 studies from where we selected the 10 most drugs studies which was tested in 170 trials as shown in the PRISMA flow diagram (Figure 1).

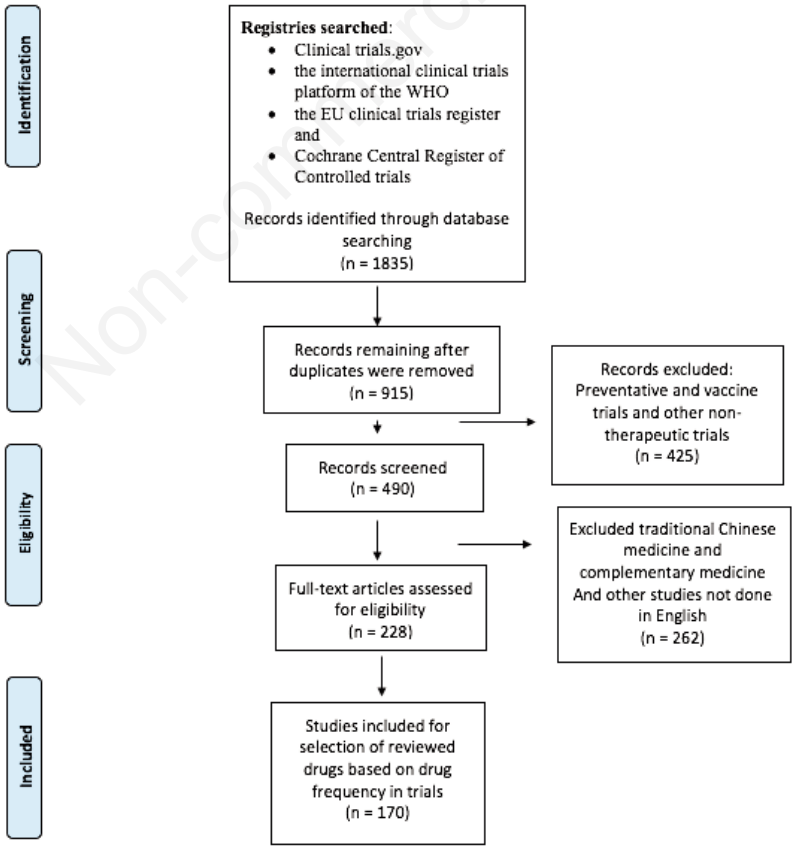

Figure 1. PRISMA flow diagram showing how the drug candidates were selected.

Data extraction

Data extraction was done using an excel spreadsheet developed for the purpose. We collected data on the trial registration, year/month of commencement, registration body, the status of the trial, type of study (vaccine trial/therapeutic trial), and the candidate drugs. We collated only the agents in the different trials and analysed them in the frequency table shown in Appendix 1 to show the most common drugs under investigation across different trials.

Results

Figure 2 shows a graph frequency of the drugs that are in the therapeutic trials while Table 1 shows the selected drugs that featured in at least 5 trials. The ten drugs are being investigated in 170 trials either independently or in combination.

Discussion

Major therapeutics in clinical trials for COVID-19 treatment

The summary of the mechanisms of action and adverse effects of the major drugs in the trials for COVID-19 is as shown in Table 2.

Antivirals

Lopinavir/Ritonavir

Lopinavir and ritonavir are protease inhibitors approved for use in Human Immunodeficiency Virus (HIV) 1. They are among the drugs being trialled for possible repurposing in COVID-19 treatment. Lopinavir/ritonavir is usually given as a combination therapy as ritonavir is said to increase the half-life of lopinavir by inhibiting the cytochrome P450 that metabolises it. Protease inhibitors generally prevent maturation of the viral particles by binding to the HIV-1 protease enzyme and preventing the cleavage of Gag-pol polyproteins (group-specific antigen-polymerase). This leads to the production of nascent immature, defective viral particles that are non-infectious.[5,13-16]

Lopinavir/ritonavir are used as combination drugs in the treatment of Human Immunodeficiency Virus-1 (HIV-1). Ritonavir increases the half-life of lopinavir by inhibiting cytochrome P450.[15]

Table 1. The most common drugs under investigation across different trials and selected drugs which featured in at least 5 trials.

S/N	Drug candidate	Number of trials
1	Ritonavir	38
2.	Lopinavir	34
3	Chloroquine/hydroxychloroquine	31
4	Interferon alpha	22
5	Remdesvir	10
6	Favipravir	9
7	Umifenovir	9
8	Darunavir	6
9	Tocilizumab	6
10	Methylprednisolone	5
	Total	170

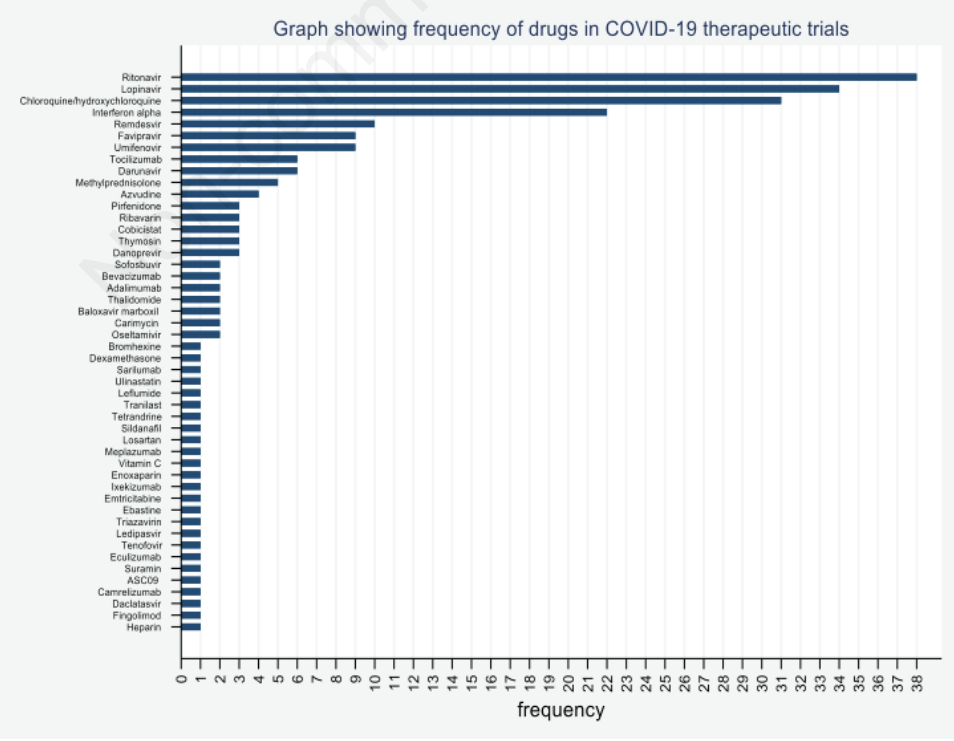

Figure 2. Frequency of drugs currently in COVID-19 therapeutic trials.

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Table 2. Summary of the mechanisms of action and adverse effects of the major drugs in trial for COVID-19.

Candidate drug	Drug class	Current indication	Mechanism of action	Adverse effects	Status of clinical trials
Lopinavir/ritonavir	Protease inhibitors (antiviral)	HIV-1	Inhibition of protease by preventing the cleavage of Gag-pol polyproteins	Nausea and vomiting Diarrheoa Anemia Hyperlipidaemia, ALT elevation Impaired cognition/memory Insomnia	On-going for SARS and COVID-19 (ChiCTR2000029539)
Chloroquine/ hydroxychloroquine	Antimalarials	Malaria Autoimmune diseases	Suppression of cytokine (TNF, IL, IFN) production/release Inhibition of viral replication.	Gastrointestinal upset Generalized pustular rash Urticaria, Erythroderma Macular retinopathy Cardiomyopathy Arrhythmias QT interval prolongation. Dizziness Tinnitus, Headaches Nightmares	On-going for COVID-19 [ChiCTR2000029609 (ICTPR); EUCTR2020-001406-27-FR]
Remdesvir	Phosphoraramidate nucleotide (antiviral)	Under trial for Ebola	Inhibition of RdRp causing premature termination of viral RNA transcription	Will likely emerge as clinical trials unfold	In phase II clinical trial for Ebola (NCT03719586); In phase III clinical trials for COVID-19 (NCT04252664)
Favipiravir	Viral polymerase inhibitior	Influenza strains unresponsive to current antivirals	Inhibition the RdRp of influenza virus (polymerase basic 1 transcriptase) thereby interfering with the viral replication	Diarhhoea Teratogenicity Increased serum uric acid levels Increased levels of transaminases Reduced neutrophil counts	In clinical trial for COVID-19 (ChiCTR2000029548)
Darunavir	Viral Protease inhibitor	HIV -1 Infection	Inhibition of protease by preventing the cleavage of Gag-pol polyproteins	Blurred vision Sweating Myalgia Constipation Diarrhoea Jaundice Facial puffiness Difficulty in breathing Vomiting Tachycardia	On-going (NCT04304053)
Umifenovir	Antiviral	Influenza	It binds directly to influenza haemagglutinin (HA) and inhibit its ability to transit to an activated conformation. It also impairs fusion by intercalation into the viral or target membrane, thereby rendering the membrane less yielding for fusion	Hypersensitivity in children	Recruiting stage of clinical trial (NCT04273763)
Interferon	Immunomodulatory (Antiviral)	Multiple sclerosis, osteoporosis, Hepatitis B and C virus infections. HPV Kaposi sarcoma	Inhibition of the activation of autophagy-inducing kinase, AMPK in viruses; it also activates macrophages that engulf antigens and natural killer cells (an immune T-cells)	Fever Myalgia Hepatopathy Difficulty in breathing Anaphylactic reactions Depression Suicidal ideation	In clinical trial for COVID-19 (PER-010-20)
Methylprednisolone	Anti-inflammatory. Immunomodulatory	Inflammatory conditions like dermatitis, Stevens-Johnson syndrome Autoimmune and aplastic anemias, nephrotic syndrome Secondary adrenal insufficiency	Binds to and activates specific receptors, resulting in altered gene expression and inhibition of pro-inflammatory cytokine production	Cataract Glaucoma Hypertension Peptic ulcer disease Pancreatitis Hyperglycaemia Hypocalcaemia Metabolic acidosis Growth suppression	On-going (NCT04263402)
Tocilizumab	Immunomodulator Anti-inflammatory	Rheumatoid arthritis Juvenile idiopathic arthritis Non-infectious uveitis	Inhibition of interleukin-6 (IL-6) binding to both membrane-bound and soluble receptors (IL-6R) in the system resulting in immunomodulation and anti-inflammation	Upper respiratory tract infections. Elevated liver enzymes Hypercholestrolaemia Gastritis Mouth ulcers Gastro-intestinal perforation.	On-going (EUCTR2020-001442-19-ES)

The adverse effects that have been reported with lopinavir/ritonavir include nausea and vomiting, diarrhea, anemia, hyperlipidaemia, Alanine Transaminase (ALT) elevation, impaired cognition or memory, insomnia and skin toxicity.[13,17-19] It is therefore instructive to be cautious in administering lopinavir/ritonavir to patients that have impaired liver functions, dyslipidaemia and psychiatric disposition.

Remdesvir

Remdesivir is an investigational drug in trial for Ebola and COVID-19. It is a phosphoraramidate nucleotide prodrug with the chemical formula: Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside. It is said has broad-spectrum *in vitro* activity against RNA viruses like Ebola, Marburg, MERS-CoV, SARS-CoV. It becomes active after phosphorylation to a triphosphate in the host's cell. Remdesivir targets the viral RNA-dependent RNA polymerase (RdRp), which is the complex protein the coronaviruses use for the replication of their RNA genomes. Its mechanism of action in human is not fully understood but *in vitro* and non-human evidence suggests that it might be that it inhibits RdRp thereby causing premature termination of viral RNA transcription process leading to termination of the overall RNA synthesis.[15,20-23]

A recent preliminary report from one the clinical trial groups for remdesvir suggests the drug caused 31% improvement in the days taken for the recovery of COVID-19 patients.[24]

However, no formal approval has been given for its use in Ebola or COVID-19 or any other disease condition.

The adverse effects of the drug will likely be emerging as the clinical trials progress.

Favipravir

This viral polymerase inhibitor is approved, in Japan, for the treatment of novel strains of the influenza virus unresponsive to current antivirals. Its activity spectrum spreads across A, B and C strains of the virus. Favipravir becomes active after ribosylation and phosphorylation. This triphosphorylated favipravir competitively inhibit the viral RNA-dependent RNA polymerase (RdRp) of influenza virus known as polymerase basic 1 transcriptase thereby interfering with the viral replication.[25-29]

Its therapeutic use, for now, is in the treatment of resistant strains of influenza virus.[29]

Favipravir is well tolerated clinically but the adverse effects that can be associated with its use include diarrhoea, teratogenicity, increased serum uric acid levels, elevated levels of transaminases, reduced neutrophil counts.[25,28,29]

Darunavir

Darunavir is a protease enzyme inhibitor with activity against HIV-1. It prevents HIV replication through binding to the enzyme, stopping the dimerization and the catalytic activity of HIV-1 protease. SARS-CoV-2 being an RNA virus also uses protease enzyme, which the drug inhibits, hence the drug is one of the antiviral candidates in clinical trial for the treatment of COVID-19.

Darunavir has bimodal activity against HIV-1 protease, enzymatic inhibition and protease dimerization inhibition. It has a high genetic barrier to the development of HIV-1 drug resistance.[30]

Ritonavir-boosted atazanavir/darunavir combination is approved for the treatment antiretroviral naïve patients in the United States of America.[31]

Adverse effects include blurred vision, sweating, increased urination, difficulty in breathing, jaundice, myalgia, facial puffiness, tachycardia, sore throat and vomiting.[32,33]

Umifenovir

Umifenovir is an indole-based hydrophobic dual-acting direct antiviral/host-targeting agent used for the treatment and prophylaxis of influenza and other respiratory infections. It has been in use in the treatment of influenza in China and Russia for so many years.[34,35] It has been reported to have inhibitory effects on a diverse array of viruses, including DNA and RNA viruses (SARS-CoV-2 is an RNA virus) as well as capsid and membrane-enclosed viruses.[34,35] Umifenovir inhibits the entry of the influenza virus at the late stage by binding directly to influenza Haemagglutinin (HA) and inhibiting its ability to transit to an activated conformation. It also impairs fusion by intercalation into the viral or target membrane, thereby rendering the membrane less yielding for fusion. Umifenovir is used therapeutically for the prophylaxis and treatment of influenza and other respiratory infections.[34,35] Major adverse effect is hypersensitivity in children. It is administered orally with an elimination half life of 17-21 hours.[34,36]

Antimalarials

Chloroquine/hydroxychloroquine (CQ/HCQ)

Chloroquine, a 9-aminoquinolne, has been in clinical use since the 20th century. Hydroxychloroquine is the hydroxylated (and safer) form of chloroquine. CQ/HCQ was approved for the treatment of malaria and autoimmune disorders like rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, etc. Its antimalarial use has been largely suspended due to resistance.[37-42]

CQ/HCQ also has interesting antiviral activities and strong immunomodulatory effects that have led to robust scientific discussions that have culminated to several trials for possible approval for treatment of emerging viral diseases like SARS-CoV-2. Its immunomodulatory effect occurs by the suppression of T-cells production/release of the cytokines - tumour necrosis alpha (TNF-α), the interleukins (IL 1, 2, 6 or 18) and interferon alpha and gamma (IFN-α,γ) which mediate the inflammatory complications of several viral diseases especially in COVID-19.

CQ/HCQ inhibits viral replication in many ways: i) inhibition of the pre-entry step of the viral cycle by interfering with viral particles binding to their cellular cell surface, ii) impairment of the early stage of virus replication by interfering with the pH-dependent endosome-mediated viral entry of susceptible viruses (like flaviviruses, retroviruses, and coronaviruses) by increasing both the endosomal and lysosomal pH leading to non-fusion with the host cell, iii) interference with the post-translational modification of the viral proteins thereby making the nascent viral particles non-infectious.[37-42]

The FDA approved CQ/HCQ include treatment of malaria (except resistant *P. falciparum* and *P. vivax* causing malaria), rheumatic disease, discoid and systemic lupus erythematosus, rheumatoid arthritis and Sjögren syndrome.[38]

Adverse effects are rarely seen with CQ/HCQ use. However, there could be gastrointestinal upset and hypersensitivity skin reactions (generalized pustular rash, urticaria, erythroderma). There are also chances of macular retinopathy, cardiomyopathy, arrhythmias, QT interval prolongation. There could also be dizziness, tinnitus, headaches and nightmares.[39,40]

Immunosuppressants/immunomodulators

Interferons

Interferons are proteins that can induce a non-specific resistance to viral infections by several mechanisms, including the inhibition of protein synthesis, inactivation of viral RNA, and enhancement of phagocytic and cytotoxic mechanisms.[43] The Interferon (IFN) system represents the first line of defence against

a wide range of viruses (in this instance, SARS-CoV-2). Viral infection rapidly triggers the transcriptional induction of IFN-β and IFN-Stimulated Genes (ISGs), whose protein products act as viral restriction factors by interfering with specific stages of the virus life cycle, such as entry, transcription, translation, genome replication, assembly and egress.[44,45]

Interferons activate macrophages that engulf antigens and Natural Killer cells (NK cells), a type of immune T-cells that are integral in the innate immune system.

The therapeutic uses of interferons include treatment of hepatitis B and C virus infection, haematological cancers, cervical cancer, anogenital malignancies, Kaposi sarcoma, chronic granulomatous disease and osteoporosis. They have also been found effective in treating asthmatic exacerbations caused by viral infection.[46]

Adverse effects include, fever, myalgia, confusion, leucopenia, elevated liver enzymes.[44,47]

Methylprednisolone

Methylprednisolone is a synthetic corticosteroid with inflammatory and immunomodulating properties which could be beneficial in reducing the massive inflammatory response that SARS-CoV-2 induces. It binds to and activates specific nuclear receptors, which have α and β isoforms. The complex formed binds to specific Glucocorticoid Response Elements (GREs) resulting in altered gene expression and inhibition of pro-inflammatory and cytokine production. This agent also decreases the number of circulating lymphocytes, induces cell differentiation and stimulates apoptosis in sensitive tumour cell populations thereby increasing survival and accumulation of neutrophils at inflammatory sites as well as induction of basophil apoptosis.[48-50]

Methylprednisolone is used therapeutically in a myriad of inflammatory conditions such as dermatitis, pemphigus vulgaris, bullous pemphigus, erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis, inflammatory bowel disease, multiple sclerosis, uveitis, scleritis, chorioretinitis, iritis and iridocyclitis, keratitis, optic neuritis, retinal vasculitis, and allergic conjunctivitis. It is also used to treat nephrotic syndrome and some inflammatory respiratory diseases, acute rheumatic carditis, acute gout, ankylosing spondylitis, dermatomyositis and polymyositis, psoriatic arthritis, rheumatoid arthritis, systemic lupus erythematosus as well as anaemias (autoimmune haemolytic and aplastic).[51]

The adverse effects are cataract, glaucoma, hypertension, pancreatitis, myopathy, osteoporosis, psychosis, hyperglycaemia, hypocalcaemia, metabolic acidosis and secondary adrenal insufficiency.[52,53]

Tocilizumab

Tocilizumab is a genetically-engineered monoclonal antibody humanized from a mouse antihuman Interleukin 6 (IL-6) receptor antibody. It has a broad-spectrum immunomodulatory activity. It inhibits IL-6 from binding to both membrane-bound and soluble receptors. IL-6 is a cytokine produced by the various immune cells in response to molecular patterns and affects multi-inflammatory cells. IL-6 is involved in differentiation of CD-4 cells into Th-17 cells that play a significant role in various immune-mediated diseases. SARS-COV-2 is thought to induce massive cytokine storm, especially IL-6, therefore, the inhibition of this IL-6 by tocilizumab significantly blocks this pathway and consequent inflammatory sequelae associated with COVID-19 disease.[54,55]

The clinical indications include rheumatoid arthritis, juvenile idiopathic arthritis and non-infectious uveitis.[54,56]

The adverse effects associated with tocilizumab include upper respiratory tract infections, elevated liver enzymes, hypercholesterolaemia, gastritis, mouth ulcers, gastrointestinal perforation.[55]

Limitations

COVID -19 is new. Trials are being registered and updated almost weekly, so it is impossible to give the most current status of therapeutic trials worldwide. We selected the most trialled drugs as at the time of initiation of review.

Some trials were conducted in languages other than English and were not reviewed.

The number of drugs under trials are too many and practically not feasible to review all in this context.

Conclusions

The race to find an effective cure for COVID-19 is on. Most of the candidate drugs in various clinical trials are being re-purposed but none has been approved as at date. It is pertinent for the bedside physicians to understand the mechanisms of action of these agents and their peculiar adverse effects so they are properly guided on the risk/benefit of the drugs they choose in managing COVID-19 patients.

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