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COMPHREHENSIVE REVIEW OF PHARMACOLOGICAL APPROCHES IN TREATMENT OF COVID'19

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Abstract

The current global pandemic, Corona viral disease (Covid-19) is an infectious disease caused by the RNA dependent virus, SARS-COV-2 which was named by WHO. There has been huge loss to life and economy because of this virus, globally. Currently, there is no vaccine to prevent or drug to cure the viral disease. However, the management of this disease is being done by using already available anti-viral drugs (Remdesvir, Lopinavir with Ritonavir) in some countries, by using anti-malarial drug (Hydroxychloroquine) or INF alpha 2B in some parts and anti-parasitic drug (Ivermectin) is being investigated in some regions of the world. Though none of the drugs are proven to be completely effective against this virus, there should be changes in the guidelines/ special guidelines of WHO for researchers to find new drugs to such newer types of viruses. As it is taking longer time to discover new drug, it is necessary to find the rational use of the above drugs in the patients. This work aims at providing complete overview of all possible COVID-19 management drugs so that it will be helpful to the researchers and healthcare professionals for the effective usage of these drugs.

Keywords: COVID-2019; SARS-Cov-2;INF-alpha 2B; Pharmacokinetics; ADR; Mechanism of Action; WHO; Anti-HIV.

Introduction

The novel corona virus[1] or SARS-Cov-2 is a great threat to life on earth. It is a zoonotic virus which is usually transferred from an animal to a human. It is a RNA virus[2] with petal or cub shaped pen liners on their surface. It has been first reported in the Wuhan state[3] of China from where it has spread to all-over the world to become a pandemic disease. This COVID-19 spreads by droplet nuclei of infected person, through air, to either directly to other people or to the innate objects from which it can again pass to the people who get in contact with the object. This disease has made mortality of more than hundred thousand all over the world and still billions of people are under life threat[4]. Still the detection of its cure is under process in various research places around the world.

Currently, the management of this disease is varying from one country to another as different medicines are being used. The medicines which are being used are either Anti-viral single therapy or combination of two Anti-viral drugs and in some places use of Anti-malarial drugs. There is a need for a discovery of novel treatment or a vaccination to this disease. But, until then the drugs that are used in the management of this disease are Lopinavir, Ritonovir, Remedisvir, Favipiravir, Interferon alpha 2b, Hydroxychloroquine and Ivermectin. These drugs are still under investigation and under management. Hence a rationalistic approach is needed for an effective management of the disease.

RITONAVIR

Introduction:
Ritonavir belongs to the classification protease inhibitor, used in intrinsic medication of viral infection. Ritonavir is a selective binder and reversible HIV

protease inhibitor that hampers with the formation of crucial proteins and enzymes, it also hampers the virus growth and causes non-functional, unfledged and non-infectious various formation.

Uses:
It is used as an Anti- HIV medication to help control HIV infection in combination with other anti-viral drugs. This is also being investigated along with other anti-viral drugs to treat COVID19[5].

Dosage:
Usually given as 200mg once a day in oral route, sometimes given along with Lopinavir as a HAART.

MOA:

Ritonavir is a protease enzyme inhibitor.

↓

In which it blocks the action of the enzyme-3chymotrypsin like protease (3CL pro) at C2 symmetric point of enzyme.

↓

There by disruption in viral replication.

ADME:
Ritonavir is highly protein bound in plasma, primarily bound to albumin & α-1 acid glycoprotein. Entire absorption is from the GI tract and increased absorption is seen with food. Time to reach plasma concentration is approximately 2-4 hours, it is distributed in CNS at minimal amount in which volume of distribution 0.16-0.66 l/kg. Plasma protein binding is approximately 98% which is broadly metabolized hepatically by CYP3A4 mainly because it is used to inhibit a particular enzyme in liver and intestine, and elsewhere and lesser by CYP2D6 iso-enzymes. The excretion is via stool where approximately 86% both unchanged drug and metabolites are eliminated. Its elimination t-half is 3-5 hours.

Adverse drug reactions[6]:
The GI adverse effects of this drug include vomiting, nausea, abdominal pain, diarrhea, anorexia and taste disorder. An over dose may lead to severe numbness, anxiety, insomnia, fever, dizziness and malaise. Renal failure with continuous dose may occur. It also reduces haemoglobin, potassium and total thyroxine level along with vasodilation change in QT wave[7]. Other events include weight loss, bronchospasm, reduced or increased WBC and neutrophil counts.

Life threatening factor:
Pancreatitis, Hepatic dysfunction, rare anaphylaxis and Stevens-Johnson syndrome are the life threatening factors.

Drug interaction:
It increases plasma concentration when taken along with one of the following drugs, **Budesonide, Fluticasone and Rivanoxaban.** It leads to increased risk in PR interval prolongation when administered with Digoxin, β-blockers, calcium channel blockers and Atazan.

Food conflict:
The absorption is increased with food. Reduction in concentration is seen with St John's Wort.

Contraindications:
The drug is contra-indicated in pulmonary hypertension.

Special warnings:
Patient with severe heart problems like Ischemia, cardiac disease, pre-existing conduction of cardio-myopathy, clotting disorder, hyperlipidemia, and pregnancy.

LOPINAVIR

Introduction:
Lopinavir[8] is an anti-retroviral agent which constrains HIV protease making the enzyme inefficient for processing of the polyprotein, resulting in production of non-infectious and immature HIV particles. The Lopinavir + Ritonavir combination (HAART) maintains the therapeutic levels.

Uses:
It is used to control the HIV infection[9] in combination with other anti-viral drugs. This drug is investigated along with other anti-viral drugs to treat COVID19[10].

Dosage:
In HIV infection, Lopinavir 400mg with Ritonavir 100mg is given twice daily. For patients who develop resistance, increase in the doses of these drugs (800mg of Lopinavir with Ritonavir 200mg) once daily is recommended.When it is taken with Amprenavir, Efavirenz, Nevirapine or Nelfinavir, the dose may be increased and it is usually administered with food.

M.O.A:

Lopinavir is a protease enzyme inhibitor

↓

It blocks the action of enzyme-3chymotrypsin like protease (3CL pro) at C2 symmetric point of enzyme

↓

There by disruption in viral replication

M.O.A of Ritonavir/ Lopinavir on COVID -19[11]:

Lopinavir/ Ritonavir is a protease enzyme inhibitor

↓

In which it blocks the action of enzyme-3chymotrypsin like protease (3CL pro)

↓

There by disruption in viral replication

Since C2 symmetric point is not seen in 3CL pro, the mechanism of Lopinavir/ Ritonavir are still under investigation on COVID-19.

ADME:

It is completely absorbed in the GI tract and the absorption is increased with food. Time taken for the drug to reach the plasma concentration is 2-4 hours approximately, it is distributed in CNS at a minimal amount in which volume of distribution 0.16-0.66 l/kg. Plasma protein binding is approximately 98% which is broadly metabolized hepatically by CYP3A4 mainly because it is used to inhibit a particular enzyme in liver and intestine, and elsewhere and lesser by CYP2D6 iso-enzymes. The excretion is via stool where approximately 86% both unchanged drug and metabolites are eliminated. Its elimination t-half is 3-5 hours.

Adverse drug reaction:

It may cause Cushing Syndrome, Hypothyroidism, Lactic Acidosis, abnormal vision, Otitis media, Tinnitus, acne, alopecia, skin discoloration, nail disorder, sweating, sex dysfunction, diarrhea, abdominal pain, asthenia, dyspepsia, vomiting and bronchitis. The acute bronchitis is generally caused when the Elimination Half-life period is 5-8 hours.

Interaction[12]:

Lopinavir level is increased by CYP3A4 inhibitors when taken with Valproate and Rifabutin.

Life threatening factor:

It may cause severe decrease in bone marrow activity which eventually results in decreased count in red blood cells, white blood cells and platelets (Myelosuppression).

Special warnings:

In Diabetic mellitus, Haemophilia A & B[13], Hepatitis, Renal impairment, Hypercholesterolemia, this drug is compulsorily used with other anti-retroviral agents in HIV treatment. Dosage forms of capsules & oral solution not interchangeable on mg per-ml basis. In pregnancy, when oral solution is used, monitor with propylene glycol-associated adverse effect.

REMDESIVIR

Introduction:

Remdesivir is an anti-viral drug which is used to treat Ebola. Also, few advancing researches say this may help in COVID-19. Certain research shows it has some effectiveness in treating the COVID-19 patients[14].

Uses:

It has been 68% effective on COVID-19 patients.

It has been generally used against the Ebola virus[15]

Dosage:

Dosing is anticipated to be twice a day to maintain the therapeutic absorption needed for the treatment of COV infections. A stream of clinical trials use an administration of 200 mg on the first day followed by 100 mg daily for consecutive days.

M.O.A:

Remdesivir blocks HIV-1 Protease enzyme

↓

Which is essential for GAG protein cleavage

↓

This results in production immature polyproteins

↓

Prevention of viral replication.

M.O.A OF REMDESIVIR ON COVID -19[16]:

When Remdesivir reaches the viral cell

↓

The viral RNA dependent RNA polymerase transfers the active Triphosphate of Remdesivir to viral RNA

↓

This causes termination of RNA synthesis

↓

This prevents viral replication

ADME:
When this drug is given at a dose of 10mg/kg in the intravenous dose to Cybnomologus monkey, it reaches the testes, epidymis, eyes and brain within 4 hours. The volume of distribution is still on the process of estimation. The half-life is 14 hours in non-human baboon. Half-life is approximately 20 hours in humans.

Adverse drug reactions:
It causes nausea, vomiting, liver damage and it affects the fetus' kidney development and it is also unsafe in lactation.

Special warnings[17]:
Remdesivir is contraindicated in severe renal failure patients and also in dialysis patients.

Interaction:
It doesn't have strong clinical investigation whether it interacts with other drug but it may be affected by some drug. Remdesivir level in the bloodstream might decrease if it is taken with antibiotics like Clarithromycin and Rifampin.

IVERMECTIN

Introduction:

Ivermectin is a semi-synthetic broad spectrum anti-parasitic drug along with anti-viral activity[18]. It has strong binding ability and particularly binds to glutamate gated Cl^- ion channels, which in turn increases the permeability of cell membranes to Cl^- ions resulting in hyperpolarisation of the nerve and the death of the parasite.

Uses:
It is used in the treatment of different types of parasitic infestations. It is still on investigation for the pharmacotherapy of COVID-19.

Dosage:
This drug is usually administered in empty stomach i.e A.C (Antecibum) 200mg OD in oral route.

M.O.A:

Ivermectin binds with high affinity to glutamated-gate cl^- channel

↓

In the smooth muscle & nerve cells

↓

Increases the permeability of cell membrane to cl^- ions

↓

Hyperpolarization and death of the parasite.

Hypothetical M.O.A of Ivermectin[19] on COVID-19:

Inhibition of Imp alpha / Beta 1

↓

Reduces the nuclear material in the virus.

↓

Causes complete eradication of genetic materials in 48hrs[19]

↓

Prevents the viral growth.

ADME[20]:
It is absorbed in the GI tract, increased absorption is seen with high fat content meal. Time to peak plasma concentration is approximately 4 hours in oral route,10 hours in topical route. Volume of distribution is 3.1 and 3.5 lkg^{-1}, after ingesting 6 and 12 mg of Ivermectin, respectively. High concentration is seen in the liver, and through adipose cell it gets into breast milk. Plasma protein metabolites are metabolized in liver by CYP3A4

enzyme. It is excreted via stool and 1% in urine. The elimination half-life period is 18 hours.

Adverse drug reaction:
It may produce edema, pruritus, urticaria rash, fever, synovitis, sore throat, cough, headache, tachycardia, orthostatic hypotension, dizziness, asthma, fatigue, somnolence, vertigo and tremor. It also causes decrease in WBC and increase in hemoglobin. It can also cause major ophthalmologic problems like burning sensation, itching and irritation in the eyes.

Life threatening factor:
Rarely Encephalopathy.

Interaction:
The metabolites interact with Warfarin and also evacuate the therapeutic value of Lacto bacillus and Estriol. It also decreases the anti-coagulation drug property and higher serum level for drugs like 4-Hydroxychloroquine, Abemaciclib, Acenocoumarol and Afatimib.

Food interactions:
The drug is generally well absorbed in oral route; the absorption is increased with high fat content meal.

Special warnings:
In patients with parasitic tropical disease, it affects skin, ophthalmic region and also conjunctiva of the eye in the immune compromised patients. This drug is also warned in pregnancy and lactation.

FAVIPIRAVIR

Introduction:
Favipiravir is an altered Pyrazine analog .It is defined to be used in resistant cases of influenza. It is generally anti-viral targeted drug for RNA –dependents[21].

Uses:
It is investigated on treatment to influenza, it acts on viral genetic matter to prevent reproduction and also it is on investigational research for pharmacotherapy of COVID-19 with some RNA genes.

Dosage:
It is given in two regimens. The first regimen is 3200mg oral loading dosage,1600mg bid on day 1 followed by 600mg bid day 2-5. The second regimen is 1800mg bid on day 1 followed by 800mg bid on daily day 2-5. Favipiravir is combined with drugs such as Tocilizumab[22] and also with Chloroquine[23] for increased effectiveness.

M.O.A:
After the viral absorption, it is bioactively changed as a nucleoside triphosphate compound which has akin structure with purine where clash the purine to inhibit RNA polymerase.

↓

It is an inhibitor for the viral enzyme RNA dependent RNA polymerase[24].

↓

Which is fundamental for viral replication

↓

Thus termination of viral replication takes place.

ADME:
Maximum plasma concentration of Favipiravir is 2 hours after the oral administration and the Half-life period is 2-5 hours in which plasma protein bindings of the Favipiravir is 54% in humans. The bound percentage of human serum albumin & α1-acid glycoprotein is 65.0% and 6.5% respectively.

Adverse drug reaction:
It causes mild to moderate diarrhea, increase in blood uric acid, transverse and decrease neutrophills count.

Drug interaction:
It causes decrease in metabolism of drugs like Warfarin and Almotriptan while decrease in elimination of Acetyldigoxin, Alprostadil, Allopurinol and Acyclovir.

HYDROXYCHLOROQUINE

Introduction:
Hydroxychloroquine is 4-aminoquinoline derivative. Hydroxychloroquine is a weak base of racemic mixture of R and S enantiomers. Chloroquine and Hydroxychloroquine are given to SARS –COV-2 patients on the basis of low micro-molar concentration, the daily dose is based on the lesion of viral load in nasopharyngeal swabs, tested in hospitals.

Uses: [25, 26]
It is used to treatment of malaria, also in certain auto immune disease (lupus rheumatoid arthritis).

Dosage:

It is wide used in oral route for prophylaxis of Malaria, Rheumatoid Arthritis, acute malaria and Chronic Auto Immune disease on skin with the dose of 400mg daily as single or as 2 divided parts of doses. For children, it is half the above mentioned dose. It is administered with food. **Over dose→** It cause many heart problems like cardiovascular collapse, rhythm and conduction disorders, then prolongation of QT waves, Torsades de points ventricular fibrillation, tachycardia. The management of over-dose includes treatment with activated charcoal and respiratory support like ventilation, incorporation of oxygen therapy.

Life threatening factors:

It may cause respiratory arrest and cardiac arrest.

M.O.A:

Hydroxychloroquine inhibits Hemozoin formation

↓

Aggregation of Cytotoxic heme

↓

Free Cytotoxic heme accumulates in parasite

↓

Causing death of Parasite.

M.O.A of Hydroxychloroquine in COVID-19:

Hydroxychloroquine

↓

Glycosylation of ACE2 turned down

↓

Attachment of virus is arrested

Assemble into acidic organells[27]→ mess with lysomes and endosomes fusion.

↓

Block the release of viral content in host cells.

Reduces IL-6 & other pro-Inflammatory cytokines.

↓

Lowers the mediators of acute respiratory Distress syndrome.

ADME:

It has an oral bioavailability[28] of 74%.The time to peak plasma concentration[29] is 3-4 hours. Generally it crosses the placenta and it also gets into the breast milk (less amount), in which plasma protein binding is approximately 40% (primarily to albumin). This is metabolized[30] in the liver to desethylhydroxychloroquine and also in small amount bisdesethylhydroxychloroquine. The excretion process by urine is 15-25% ≤60% as constant drug elimination half-life period is 40 days for 200mg.

Adverse drug reaction[31]:

It produces Throbbing in ears, weight loss, abdominal pain, nausea, vomiting, nervousness, itching, and rashes in skin. Over dose may lead to mood swings, light sensitivity, convulsion. Still some ADRs are unknown for this drug due improper clinical evidences.

Interactions:

Hydroxychloroquine may augument the effect of anti – diabetic agents, resulting in fluctuation of blood glucose level. It also increases the plasma digoxin level, boosts the risk of Trosade De Point with QT wave prolongation when taken with Quinidine, Amiodarone, Sotalol and Disopyramide. It also increases the risk of convulsion with Mefloquine. Sometimes antacids inhibit the hydroxychloroquine retention. In pregnancy, care is taken until the capable benefit is seen because it causes risk to foetus.

Special warnings:

It is anticipated to cause pathological changes to the macula, an area at the point of retina which is immensely sensitive and provides accurate vision.

Interferon Alpha-2b:

Introduction

Interferon Alpha 2b (IFN alpha-2b) is a recombinant interferon which was originally produced from E-Coli to be used as an anti-viral[32] and anti-neoplastic agent.

Dosage[33]:

Interferon alpha 2b is usually given up to 5000 IU/ml in intranasal route.

Adverse drug reaction:

It may cause Abscess or other reactions at the injection site. Other ADRs include increase in body temperature, decreased sleep, nausea, vomiting, behavioral or mood changes.

M.O.A:

Two mechanism[34] of action is seen- it acts directly and indirectly on reducing the viral replication.

Direct method

Interferon alpha-2b causes

↓

Cell cycle apoptosis

↓

Cell cycle arrest.

Indirect method

Activation of T-cells and NK cells.

↓

Induction of cytokine

↓

Activation JAK-STAT pathway

↓

Regulation of gene expression

↓

Anti-proliferation effect on the cell.

Pharmacokinetics

Interferon alpha-2b absorption is slow in Intramuscular and Sub-cutaneous route of administration, with absorption t-half of 5.8 and 5.5 hours, respectively. The maximum after administration is found to be 42.1 IU/mL at 6hours in IM route and 45.8 IU/mL at 8 hours in SC route.

Special warnings

Do not use interferon alfa-2b, if patients have Auto-immune Hepatitis, or Chronic Liver Diseases other than Hepatitis B or C. Avoid using in Pregnancy and if you are planning for pregnancy avoid the drug before 6 months.

Interaction

Don't combine with Ribavirin if you are pregnant, or if your sexual partner is pregnant.

CONCLUSION

The use of anti-viral drugs as a prophylactic will be effective in the people with recommendations from health care professionals for those who are very prone to this virus in the absence of vaccine, but the self-medication of COVID-19 management are seen in some regions of the world which is a severe threat to life of the patients. At this pandemic time, people must follow only the guidelines given by healthcare professionals and take medicines only on their advice. The rational use of drugs is a key to combat the disease, hence complete knowledge about the drug including its ADR and the special warnings have to be made available for the healthcare professionals and researchers, so that the best possible management of SARS-Cov-2 can be achieved. Based on this review, it can be concluded that the individual or combination of these drugs are not found to be completely safe and effective in COVID-19 management. Hence it is required to develop a newer drug or vaccine in Allopathic System of Medicine and also other system of medicines like Chinese medicine, Sidhha system, Ayurvedic System and Homeopathic system has to be investigated and researched for availing the relief from the novel corona virus-2019.

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