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- To extend viable outreach programs for the health care need of the society.
- To develop industry institute interaction and foster entrepreneurial spirit among the graduates

AGENTS OR DRUGS WITH POTENTIAL ACTIVITY AGAINST SARS- n Covid-19

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The severe acute respiratory syndrome coronavirus 2 (SARS – CoV – 2) outbreak has spread to many countries and caused thousands of cases and deaths. Most people who are infected get mild respiratory symptoms that disappear, but some develop severe illness. The virus is transmitted through contact with an infected person or via respiratory droplets when an infected person sneezes or coughs. There is a higher risk if one suffers from any comorbidities already. The purpose of this newsletter is to provide relevant information regarding to the various options of drug therapy on COVID – 19 pandemic.

Though there are no specific therapies approved by the US FDA for SARS – CoV – 2, there are many agents under investigation based on invitro studies that shown activity against SARS – CoV – 2 or related virus. This article provides information regarding to these agents.

Generally, pharmacologic treatment is not recommended for young, healthy patients with mild symptoms and no underlying comorbid conditions.

Agents or drugs with potential activity against SARS – CoV – 2:

Remdesivir:

Classification: Nucleoside analogue (broad spectrum antiviral).

Usage: The EUA (Emergency Use Authorization) allows for the emergency use of remdesivir to treat suspected or confirmed COVID-19 in adults and children hospitalized with severe disease.

Mechanism of action: Remdesivir is a monophosphoramidate prodrug of remdesivir-triphosphate (RDV-TP), an adenosine analog which acts as an inhibitor of RNA-dependent RNA polymerases (RdRps). RDV – TP competes with adenosine-triphosphate for incorporation into viral RNA chains. Once incorporated into the viral RNA, it terminates RNA synthesis by evading proofreading by viral exoribonucleases.

Safety concerns:

- Caution in patients with renal impairment due to formulation with sulfobutyl ether beta-cyclodextrin sodium (SBECD).
- Hypersensitivity and infusion-related reactions.
- Risk for elevated hepatic enzymes.

Chloroquine & Hydroxychloroquine:

Classification: Antimalarial

Usage: On June 15,2020, FDA decided for authorized use of this drug for the treating COVID – 19, also, in light of ongoing serious cardiac adverse events and other serious side effects. And the EUA stated that treatment was for adult and adolescent patients weighing 50 kg or more who were hospitalized with COVID-19.

Mechanism of action: Various mechanisms that may include inhibition of viral enzymes, viral protein glycosylation, virus assembly, ACE2 cellular receptor inhibition, acidification at the surface of the cell membrane inhibiting fusion of the virus, and immunomodulation of cytokine release.

Safety concerns:

- Use in COVID-19 patients outside of clinical trials or in a nonhospital setting is not recommended due to the potential for serious adverse events and drug interactions.
- Risk of cardiac arrhythmias (e.g., QT prolongation, arrhythmias)
- Risk of retinal damage, especially with long term use.

Lopinavir & Ritonavir:

Classification: HIV protease inhibitor

Mechanism of action: these drugs bind to M^{pro}, a key enzyme for coronavirus replication and may suppress coronavirus activity.

Safety concern:

- Risk of cardiac arrhythmias, QT prolongation
- Caution in patients with hepatic disease or hepatitis
- Significant drug interactions

Favipiravir:

Classification: RNA-Dependent RNA Polymerase Inhibitor (broad spectrum antiviral)

Usage: It is advised to used in the patients with mild to moderate disease condition.

Mechanism of action: Favipiravir is an RNA-dependent RNA polymerase (RdRp) inhibitor that inhibits viral RNA synthesis.

Safety concern:

- Contraindicated in pregnancy due to early embryonic death and teratogenicity.

Supportive therapy

Azithromycin:

Classification: Macrolide antibacterial

Usage: Azithromycin may prevent bacterial superinfection, and macrolides may have immunomodulatory properties to work as adjunct therapy.

Mechanism of action: Macrolides have immunomodulatory properties (reducing chemotaxis of neutrophils (PMNs) to the lungs by inhibiting cytokines (i.e., IL-8), inhibition of mucus hypersecretion, decreased production of reactive oxygen species, accelerating neutrophil

apoptosis, and blocking the activation of nuclear transcription factors) in pulmonary inflammatory disorders. They down regulate inflammatory responses and reduce the excessive cytokine production associated with respiratory viral infections; however, their direct effects on viral clearance are uncertain.

Safety concern:

- Risk of cardiac arrhythmias (e.g., QT prolongation)
- Significant drug interactions.

Anticoagulants:

- Venous thromboembolism (VTE) prophylaxis with LMWH is recommended for all hospitalized patients with COVID-19 infection. Withhold VTE prophylaxis for active bleeding, platelet count less than 25 x 109/L, or fibrinogen less than 0.5 g/L
- In acutely ill hospitalized COVID-19 patients, anticoagulant prophylaxis with LMWH (Low Molecular Weight Heparin) or fondaparinux is recommended.
- In critically ill COVID-19 patients, anticoagulant prophylaxis with LMWH is recommended over UFH (unfractionated heparin); LMWH or UFH is recommended over fondaparinux or DOAC (Direct Oral Anticoagulant).
- Therapeutic-intensity anticoagulation is not recommended in the management of COVID-19 in the absence of confirmed or suspected VTE outside of a clinical trial.
- Increasing the intensity of anticoagulation (i.e., from standard-intensity prophylaxis to intermediate-intensity prophylaxis or from intermediate-intensity prophylaxis to therapeutic-intensity prophylaxis) is advisable in COVID-19 patients who experience recurrent clotting of access devices or extracorporeal circuits.

Corticosteroids (Dexamethasone):

Usage: It is recommended to use dexamethasone for up-to 10 days in COVID – 19 patients who are mechanically ventilated and who require supplement oxygen but not ventilated.

Mechanism of action: Corticosteroids are endogenous hormones produced in the adrenal cortex or their synthetic analogues. The 3C – like proteinase on SARS – CoV – 2 inhibit HDAC2 (histone deacetylase 2) transport into the nucleus, and so impairs the way in which it mediates inflammation and cytokine responses, so activation of histone deacetylase by dexamethasone may directly oppose the action of SARS – CoV – 2.

Safety concern:

- Contraindicated in systemic fungal infections, hypersensitivity
- Caution in Congestive heart failure, diabetes mellitus, epilepsy, glaucoma, hypothyroidism, psychiatric adverse effects

Convalescent plasma:

Classification: Plasma collected from persons who have recovered from COVID-19 that may contain antibodies to SARS-CoV-2.

Usage: Clinical trials are being conducted to evaluate the use of convalescent plasma in the treatment of severe or immediately life threatening COVID – 19 patients.

Pulmonary vasodilators:

- There is no evidence for rational use of inhaled pulmonary vasodilators like nitric oxide in acute respiratory failure in COVID – 19. Avoid aerosolized vasodilators.
- Additional data regarding clinical efficacy for COVID – 19 are being evaluating.

Fibrinolytics:

Usage: Recommended to use in the COVID patients with prothrombotic presentations, normal lung compliances on the ventilator, and high alveolar – arterial oxygen gradients, COVID – 19 infection associated with coagulopathy could potentially be considered for fibrinolytics. Fibrin deposition in the pulmonary microvasculature is a causative factor in the development of ARDS (Acute Respiratory Distress Syndrome).

Mechanism of action: These agents act by converting plasminogen to plasmin on the surface of existing thrombi, thereby initiating local fibrinolysis.

Safety concern:

- Bleeding

Interleukin – 1 (IL – 1) antagonists (Anakinra):

Usage: Used in cytokine release syndrome may be component of severe diseased condition of COVID – 19 patients.

Mechanism of action: These prevent the binding of IL – 1 to its receptors. Anakinra acts similarly to the native interleukin-1 receptor antagonist by competitively inhibiting the binding of both IL-1 alpha and IL-1 beta to the IL-1 type 1 receptor.

Safety concern:

- Caution in patients with thrombocytopenia and neutropenia
- Infusion – related reactions

Interleukin – 6 receptor antagonists (Siltuximab, Tocilizumab):

Usage: Used in cytokine release syndrome may be component of severe diseased condition of COVID – 19 patients.

Mechanism of action: Interleukin – 6 is a proinflammatory cytokine that is involved in various processes like T – cell activation, hepatic acute – phase protein synthesis initiation etc., These agents block IL – 6 mediated signaling by competitively binding to both soluble and membrane bound IL – 6 receptors and thus calms the aberrant hyper immune response called cytokine strom.

Safety concern:

- Caution in patients with thrombocytopenia and neutropenia.
- Risk of hepato-toxicity, GI perforation
- Infusion related reactions

Janus kinase (JAK) inhibitors (Baricitinib, Ruxolitinib):

Usage: Used in cytokine release syndrome may be component of severe diseased condition of COVID – 19 patients.

Mechanism of action: The JAK – mediated signaling is pivotal in influencing immune system activation, as cytokine receptors are expressed on most immune cells. These inhibitors regulate the signaling pathway by preventing the phosphorylation and activation of STATs (Signal Transducers and Activators of Transcription proteins).

Safety concern:

- Caution in patients with neutropenia, lymphopenia and anemia
- Risk of GI perforation
- Monitor for elevated liver function tests
- Thrombosis, including deep vein thrombosis and pulmonary embolism

NSAIDs:

- According to NIH COVID – 19 treatment guidelines there is no difference in the use of antipyretic treatments between patients with or without COVID – 19 patients. Patients who are taking NSAIDs for comorbid conditions should continue therapy as previously directed by the prescriber.