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The Most Commonly Used Drugs in Combating the Emerging Corona Virus Disease (Covid-19)

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Abstract : "Covid-19 (coronavirus disease 2019) is a global public health crisis." There is no successful accepted prescription until recently, but researchers are rushing to find a cure for patients, particularly those who have other underlying disorders or develop a severe form of the disease. The purpose of this study is to establish the facts regarding COVID-19 as much as it is a practical treatment. In this study, we talk about some of the drugs that were used to treat patients infected with the Coronavirus. Some of these drugs had effective results in reducing serious symptoms, such as dexamethasone, and some of them were banned after several trials.
Keywords : Covid-19, Treatment, Drugs, coronavirus, Dexamethasone.

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Introduction

"Coronaviruses (CoV) are a large group of viruses that have the capacity to cause infections ranging from the common cold to diseases of higher severity such as Severe Acute Respiratory Syndrome (SARS-CoV-(1) and the Middle East Respiratory Syndrome (MERS-CoV)". "COVID-19 pandemic causative agent is SARS-CoV-2, a non-segmented, positive-sense RNA virus closely related to SARS-CoV-1, as it shares 82 per cent of nucleotide identity. here is no approved full therapy or deeply evaluated treatment guidelines for COVID-

19."Most of the recognized researches that suggest a potential treatment for COVID-19 were based on the experience with MERS, SARS, or limited to case-series". Randomized-controlled clinical trials (RCT) are proceeding, most remarkably with two particular agents, the novel investigational antiviral remdesivir and the antiretroviral lopinavir-ritonavir (Kaletra®) Known for HIV Care. Non-randomized smaller studies, primarily from China, have involved several drugs, with Chinese Medicine research covering over half of the researches. *In vitro* data and preclinical studies of various agents, predominantly from the treatment of severe acute respiratory syndrome, have also been published. The discussion regarding potential treatment for COVID-19 within the medical community is taking place mostly through non-academic channels such as the news, social media, or blogs". Table .1 highlights scientific researches on possible treatments of COVID-19 and other coronaviruses. (1)

Table 1: Some Possible Medicines for COVID 19 Treatments. (1)

Drugs	Role in the treatment of COVID-19
Dexamethasone	"In this review, we emphasize the importance of dexamethasone and its role in the treatment of COVID-19. Dexamethasone reduces morbidity and mortality in COVID-19 patients requiring respiratory support, as it prevents tissue damage and attenuates the severity of inflammation. Timely initiation of short-course dexamethasone, a low-cost and relatively low-risk intervention may help prevent the progression of hypoxic respiratory failure in moderate to severely ill patients and help accelerate recovery" (2).
"Lopinavir; Ritonavir"	"The role in the treatment of COVID-19 is unclear. Preclinical data indicated a potential benefit; however, data that is more recent has failed to confirm the efficacy".
"Remdesivi"	"Investigational and only available through expanded access and research protocols; numerous large clinical trials are in progress".
"Chloroquine/Hydroxychloroquine"	"In vitro and limited clinical data suggest potential benefit".
"Oseltamivir"	Assistant factor
"Ribavirin and interferon"	Assistant factor
"Tocilizumab"	"A drug for immunomodulation, its use in some protocols are linked to theoretical mechanisms and limited preliminary data as an adjunct therapy".
"Azithromyci"	"Employed in some protocols, its use is linked to theoretical mechanisms and limited preliminary data as an adjunctive treatment".
"Corticosteroids"	Assistant factor
"Antibiotic therapy"	Assistant factor
"NSAIDs/Ibuprofen"	Assistant factor

1. Dexamethasone

1.1 Recommendations: Recommended for use in severe cases that require ventilation, as this study is still recent

1.2 Classification: A corticosteroid (specifically a glucocorticosteroid) that has numerous uses in treating cancer. One of the ways it works is to reduce inflammation (swelling) and treat emergency cases infected with the Coronavirus.

1.3 The reasoning for use: The World Health Organization (WHO) welcomes the initial clinical trial results from the United Kingdom (UK) that show dexamethasone, a corticosteroid, can be lifesaving for patients who are critically ill with COVID-19. For patients on ventilators, the treatment was shown to reduce mortality by about one third, and for patients requiring only oxygen, mortality was cut by about one fifth, according to preliminary findings shared with WHO.(3)

1.4 Mechanism of Action: It is known as an immunosuppressive and anti-inflammatory agent. It binds to the glucocorticoid receptor(GR) and mediates changes in gene expression leading to numerous downstream effects from hours to days. (5) It acts by suppressing migration of neutrophil and decreasing lymphocytes proliferation. Stability of the lysosomal membranes have increased, and the capillary membrane is becoming less permeable. Higher concentrations of vitamin A compounds are present in the serum, and prostaglandin and some cytokines such as (interleukin-1, interleukin-12, tumor necrosis factor interleukin-18, interferon-gamma, and granulocyte-macrophage colony-stimulating factor) are inhibited (5). It inhibits pro-inflammatory targets with a varying degree; Cyclooxygenase-2 (CXO-2), interferon-gamma, interleukin -1α, and interleukin -1β are strongly inhibited while, C-X-C motif ligand (CXCL1), CC motif ligand 3 (CCL3), interleukin -6, and interleukin -1Ra are less strongly inhibited (5). Dexamethasone may also improve pulmonary circulation and increase surfactant levels (4). "Lower doses of corticosteroids have anti-inflammatory effects, whereas higher doses are immunosuppressive" (4) (6) (76) (77)

1.5 Evidence / Experience:

- "There is little evidence of benefit from glucocorticoids in general or dexamethasone in particular in viral infections other than COVID-19".
- "Shang et al published the views of Chinese experts who had treated COVID-19 in Wuhan. They stated that "systemic corticosteroids should probably not be used for the treatment of COVID-19. For critically ill patients with ARDS at an early stage, corticosteroids should probably be prudently used at a low or moderate dose over the short course if there are no contraindications (Grade 2–, weak recommendation)."
- "We now have preliminary results from the dexamethasone arm of the UK RECOVERY Trial. The NHS Central Alerting System posted a letter from the UK's four Chief Medical Officers and the Director of NHS England, providing scanty details: "Dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days was compared with 4321 UK patients randomised to usual care alone. Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; P=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; P=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75; P=0.14)." The Press Release from the investigators clarified one of the problems with this letter, making it clear that 2104 patients had been randomized to dexamethasone treatment".(7)

1.6 Safety Concerns: "Dexamethasone is generally safe. It presents a favourable benefit-risk profile, particularly in patients with severe forms of pneumonia, while the benefit is less prominent in patients with non-severe pneumonia. As the treatment is short, even at high doses, corticosteroids are not associated with serious side effects".(8)

2. Lopinavir/Ritonavir

2.1 Recommendation: Recommended against its routine use outside randomized controlled trials.

2.2 Classification: "HIV Protease Inhibitor".

2.3 The reasoning for use: "experimental animals and In vitro investigations reveal potential activity on other coronaviruses (MERS-CoV and SARS-CoV)".(9) (10) (11) (12).

2.4 Mechanism of Action: "Ritonavir and lopinavir may attach to Mpro, a crucial enzyme in the replication process of coronavirus".(13)

2.5 Evidence / Experience

- Animal research reveals behavior for other coronaviruses.(9) (10) (11) (12)
- "An open-label randomized controlled trial involving hospitalized patients with a defined SARS-CoV-2 infection (n=199), analyzed for ritonavir therapy; lopinavir". (14)
- "Treatment with ritonavir; lopinavir for two weeks was not associated with a difference from the standard of care over time to clinical improvement (hazard ratio 1.24; 95 % CI, 0.9 to 1.72)".
- The 28-day mortality rate was considered to be close between study groups (19.2 percent vs. 25 percent , respectively).

- There was similar proportion of patients carrying detectable ratio of viral RNA. “In a modified intention-to-treatment analysis, lopinavir; ritonavir showed a median time to clinical improvement that was shorter by one day” (hazard ratio, 1.39 per cent; 95 per cent CI, 1 to 1.91).
- “A previous retrospective cohort study of inpatients reviewing the clinical course and risk factors for mortality included 29 patients who treated with lopinavir; ritonavir”.(15)
- “There was no difference in the length of lopinavir viral shedding; ritonavir therapy”.
- “Comment: ESICM and SCCM Surviving Sepsis Campaign recommend against the routine use of the combination in critically sick adults”.(16)

2.6 Safety Concerns: (17) (18).

1. Caution in hepatic disease patients.
2. "Risk of cardiac arrhythmias (e.g., prolonged QT)".
3. "Significant drug interactions".

“They are an antiviral drug combination employed in the treatment of human immunodeficiency virus”. “Lopinavir has the capacity to inhibit the protease activity of coronavirus while ritonavir rises the half-life of lopinavir”. “Lopinavir/ritonavir is accessible in Canada, which gives it more advantage, and has a recognized toxicity profile”. “In BC, the agent is considered as non-formulary medicine as it obtained mostly from the Centre for Excellence for the treatment of HIV”. “Meanwhile, it is listed under “No Stock Available” item, but it potentially could be acquired by other channels”. “Ribavirin may exert synergistic properties when added to lopinavir/ritonavir, particularly in other the other viruses of the family”. “However, most clinical data available for COVID-19 does not suggest the routine addition of ribavirin”. “Oral ribavirin is accessible in Canada and is presently non-formulary. Inhalational ribavirin is used only for the treatment of RSV but has not been assessed for coronaviruses”.

3. Remdesivi

3.1 Recommendation: Recommended outside a randomized controlled trial against its routine usage.

3.2 Classification: “Investigational Nucleoside Analogue”.

3.3 The rationale for Use: “The principle is that remdesivir is considered as a broad-spectrum antiviral drug with in vitro activity against coronaviruses”.(19)(20)(21)(22)(23)(24)(25)(26).

3.4 Mechanism of Action: “It is a monophosphoramidate prodrug that is metabolized to remdesivir-triphosphate (RDV-TP), which is an analog of adenosine which can inhibit the function of RNA-dependent RNA polymerases (RdRps). Remdesivir-TP is a competitor of adenosine triphosphate for the combination with the nascent viral RNA chains. When it binds into the viral RNA at the position i, RDV-TP suppresses RNA synthesis at position i+3. Because RDV-TP does not cause instant termination of the chain (i.e., three more nucleotides are integrated after RDV-TP), the drug seems to escape from the viral exoribonuclease, which is an enzyme that has the ability to conduct a proofreading process to remove nucleotide analog inhibitor”. (19)(20) (21)(22)(23)(24)(25)(26)(27).

3.5 Evidence / Experience

- “Remdesivir has been given to a number of patients diagnosed with severe SARS-CoV-2 infection in the US, Japan, and Europe throughout Compassionate Use programs”. (28).
- “Remdesivir has shown substantial action against coronavirus and a strong genetic barrier to resistance in preclinical studies”.(19) (20).
- “outside a randomized-controlled trial data concluded that remdesivir has an antiviral properties with a powerful action against clinical SARS-CoV-2 isolate; [half-cytotoxic concentration (CC50) over 100 mcgM, half-maximal effective concentration (EC50) = 0.77mcgM, selective index (SI) more than 129.87”.
- “The data reveal that remdesivir (GS-5735) prevents the activity of MERS-CoV, 2002 SARS-CoV, and bat CoV strains that have the potential to infect humans and replicate in epithelial cells after they penetrate through CoV receptors”.

- In an experimental mouse model, Remdesivir demonstrated therapeutic and prophylactic efficacy as against 2002 SARS-CoV.
- "Mutations with resistance have not been recognized".
- "Many clinical trials estimating the effectiveness of remdesivir in patients with SARS-CoV-2 infection are being carried. Data from some trials are expected by April 2020".(28).

"Remdesivir is an investigational broad-spectrum antiviral nucleotide analog. It was originally evaluated and developed for the treatment of Ebola. It acts by inhibiting the RNA-dependent RNA polymerase, which is 96% matching in sequence with MERS, COVID-19, and SARS. Remdesivir has manifested in vitro and in vivo activity against SARS and MERSviral pathogens". (29).

"Unfortunately, the drug is not approved by the FDA yet. It was used for one of the first patients infected with COVID-19 in the US on the basis of Compassionate Use (CU)". (30) "The results were benefit which the symptoms disappeared swiftly within one week of therapy and no side effects were recorded. Viral PCR test gave a negative result for the virus following one day of treatment".

"In the US, the drug is being used in different stage three trials sponsored by NIAID. Recording to such a study appears like the desired approach to antiviral treatment but it is not applied in Canada at the main time. Moreover, there are other four trials taking place worldwide".

"Health Canada and the company (Gilead) have established the process of obtaining remdesivir in Canada for CU outside of the aforementioned RCT. It involves a multi-step procedure that comprises the Special Access Program (SAP) to Health Canada as well as an application on the Gilead website. The estimations are that making remdesivir available would take a couple of days and is not confirmed. Personal communication found that one group in Edmonton tried to obtain the drug for CU; it was never received or released from the company. The inclusion criteria for its use appear prohibitive; patients are required to be diagnosed with serious viral disease failing supportive care, on ventilatory support but not receiving vasopressors medications or suffering from organ failure. The employment of CU and SAP may be considered if the eligibility criteria are present. Gilead stated on their official website that their stock was insufficient and they were unsure if the drug would be provided free of charge. There are also modifications upcoming to the Gilead program. The CU program is transforming into an expanded access program. It is undefined how this will affect the access of remdesivir in Canada".

4. Chloroquine/Hydroxychloroquine

Recommendation: Recommended against their use for the prophylaxis or treatment outside of a clinical study.

4.1 Chloroquine:

Classification: The Antimalarial Agent.

The reasoning for use: "the drug has in vitro antiviral properties against SARS-CoV-2 and may reveal immunomodulating results".(31)(32)(33)(34).

Mechanism of Action: the mecanisms may involve the inhibition of the activity of viral enzymes such as viral protein glycosylation, viral DNA or RNA polymerase, virus assembly, as well as virus release. Other processes may also include; acidification at the surface of the cell membrane inhibiting fusion of the virus, ACE2 cellular receptor inhibition, and the immunomodulation of cytokine release".(32)(33) (35) (36)(37)(38)(39)

Evidence / Experience:

- Animal studies indicate that chloroquine has anti-SARS-CoV-2 activity.(31)(32)(33).
- "Numerous reports state that the exacerbation of pneumonia is inhibited in patients with SARS-CoV-2 infection; however, the data available are insufficient".(31)
- "Several protocols involved recommendations for use".(40) (41) (42).
- "Further data concerning clinical efficiency for COVID-19 are being assessed".(43)(37).

"Safety Concerns": (44) (18)

1. "The risk of cardiac arrhythmias especially QT prolongation".
2. "The risk of retinal damage, particularly with chronic use".
3. "Extra caution is needed for patients living with G6PD deficiency".
4. "More caution with diabetic cases".
5. "Major drug interactions".

4.2 Hydroxychloroquine

Classification: Antimalarial

The reasoning for use: "The drug has in vitro antiviral potential against SARS-CoV-2 and may result in an immunomodulating effect".(31) (32) (33) (34).

Mechanism of Action: "Strategies may involve the inhibition of the activity of viral enzymes such as viral protein glycosylation, viral DNA or RNA polymerase, virus assembly, as well as virus release. Other processes may also include; acidification at the surface of the cell membrane inhibiting fusion of the virus, ACE2 cellular receptor inhibition, and the immunomodulation of cytokine release".(32) (33) (35) (36) (37) (38) (39).

"Evidence / Experience"

- "Animal studies indicate that the drug is active against SARS-CoV-2".(40)(33)(34)(45)(41).
- "Single in vitro study showed that Hydroxychloroquine may have more significant antiviral activity in comparison with Chloroquine".(33).
- Hydroxychloroquine manifested more potent in vitro antiviral potential in contrast to Chloroquine.
- The EC50 values for Chloroquine exceeded 100 microM in one day and 18.01 microM in two days.
- The EC50 results for Hydroxychloroquine were 6.25 microM in one day and 5.85 microM after two days.
- "An open-label non-randomized clinical study involved 26 patients treated with Hydroxychloroquine and negative control group".(46).
- "Preliminary data revealed the number of cases who had negative PCR test results varied significantly between the treated and untreated groups".
- "On the sixth day of therapy, 70% of the patients treated with Hydroxychloroquine were completely free of detectable viral load compared with the control group (12.5%)".
- "Several protocols involved recommendations for use".(40) (41).
- "Further data concerning clinical efficiency for COVID-19 are being assessed".(43) (37).

"Safety Concerns": (47) (18)

1. The risk of retinal damage, particularly with chronic use.
2. The risk of cardiac arrhythmias especially QT prolongation.
3. Extra caution is needed for patients living with G6PD deficiency.
4. More caution with diabetic cases.
5. Major drug interactions.

"Hydroxychloroquine and chloroquine are commonly utilized for the treatment of rheumatoid arthritis, amebiasis, and malarial infections. Both have in vitro anti-viral properties, but no confirmed clinical efficiency in the treatment of viral infections. The drugs seem to exert their actions through several processes involving glycosylation of the ACE2 receptors thus weakening SARS-CoV-2's capability to diffuse into cells, disturbance of the acidification of endosomes thereby inhibits the trafficking of the virus within cells, as well as immunomodulatory actions, that may reduce cytokine release in critical cases. However, it should be taken into account that immune-compromising properties might be a drawback when it comes to viral disease".

"Chloroquine is presently inaccessible for order in Canada, while Hydroxychloroquine is obtainable and on the BC provincial formulary. However , as a result of the strong worldwide request of Hydroxychloroquine after the announcement made by President Trump's press release on March 19, 2020, calling it a "game-changer".

"The safety of the therapy with this drug has not been evaluated in the case of coronavirus infections. However, its use is well tolerated in patients suffering from rheumatoid arthritis or malaria. Common adverse reactions involve gastrointestinal intolerance, while some patients may experience uncommon side effects such as skin reactions and hypoglycemia. Other rare symptoms may be encountered as results of the drug toxicity include bone marrow suppression, cardiac arrhythmias and, hepatotoxicity. Retinal damage is a recognized side effect of Hydroxychloroquine but typically caused after years of chronic use".

5. Oseltamivir:

5.1 Recommendation: Recommended against the use of the drug unless it was assumed or diagnosed to be an influenza infection.

5.2Classificatio: Neuraminidase Inhibitors.

5.3 The reasoning for use: The treatment of influenza symptoms.

5.4 Mechanism of Action: "Oseltamivir phosphate is metabolized into the active form oseltamivir carboxylate, which is a selective potent suppressor of neuraminidase enzymes of the influenza virus". The action of the viral neuraminidase enzyme is essential to gain entry into other healthy cells, for the release of nascent virus particles from the injured cells, and for the spread of the infection throughout the body. (41) (33) (42). Oseltamivir action declines the infectivity by reducing the viral shedding. Oseltamivir is active against influenza A (involving H1N1) and influenza B viral neuraminidases.(41) (33) (42).

5.5 Evidence / Experience:

- Trials indicate a higher risk of suffering from emitting and nausea.
- To back up claims that it lessens complications of influenza and admissions to hospital.
- In conclusion, Oseltamivir is used for the prophylaxis or treatment of influenza A infection in aged persons. (48).
- The drug is a well-tolerated oral neuraminidase suppressor that profoundly decreases the period of the symptoms and accelerates the return to the ordinary activity levels of patients with influenza that is naturally acquired.
- Oseltamivir represents a suitable therapeutic substitute to zanamivir (particularly in persons who prefer to take the treatment orally or suffer from an underlying respiratory condition)

5.6 Safety Concerns:

1. The flu vaccine is not used within two days after having the medicine.
2. The medicine is not given if the patient is allergic to it. The doctor is informed if there is kidney disease.
3. Category C drug, it is not known whether the medicine is teratogenic or not.

"Neuraminidase suppressors do not appear to be active against COVID-19 (49). In case of critically ill patients, Initial empiric treatment with neuraminidase inhibitors is reasonable throughout the period of influenza season. If the patient is suspected to have influenza pneumonia, nasopharyngeal swabs is taken to test for influenza. Presently, in many situations, patients diagnosed with viral pneumonia is much more likely to be influenza infection rather than COVID-19. The role for the drug especially for COVID-19 is limited".

6. Ribavirin and interferon:

6.1 Recommendation: Recommended against their use for risk of harm.

6.2 Classification: "Synthetic guanosine nucleoside analogue and antiviral agent that interacts with the process of viral mRNA production".

6.3 The reasoning for use: Chronic infection of hepatitis C.(50).

6.4 Mechanism of Action: "Mechanism: Ribavirin acts by several processes that eventually lead to the suppression of viral RNA and protein synthesis". "Adenosine kinase converts it to ribavirin mono-, di-, and triphosphate forms". "Ribavirin triphosphate is the major active metabolite that interfere with the viral mRNA polymerase by preventing the nucleotide binding site of the enzyme, causing a decrease in the stage of replication or production of defective viral particles"(51) . "It also inhibits the functions of viral mRNA 2′-O-methyltransferase and mRNA guanylyltransferase of dengue virus". "The Suppression of these enzymes interrupts with the posttranslational step of capping the 5′ end of viral messenger RNA by ribavirin being integrated at the 5′ end in the position of guanosine and prevents the cap methylation stage".

Inosine monophosphate dehydrogenase (IMPDH) inhibition and subsequent reduction of guanosine triphoshpate (GTP) pool is another proposed mechanism of ribavirin. Throughout guanosine monophosphate (GMP) synthesis, IMPDH initiates the rate-limiting step in which inosine 5′-monophosphate is transformed to xanthine monophosphate. Then the conversion of GMP to GTP takes place. Ribavirin monophosphate closely matches the structure of inosine 5′-monophosphate and functions as a competitive inhibitor of IMPDH. The inhibition of de novo synthesis of guanine nucleotides and the reduction of intracellular guanosine triphoshpate pools limit the viral protein synthesis as well as the replication of viral genetic materials (51).

Ribavirin increases viral mutations by acting as mutagen to the target virion to cause an 'error catastrophe'. RTP couples with uridine triphosphate or cytidine triphosphate with the same efficiency and inhibits HCV RNA elongation. Thus, it causes a premature termination of HCV RNA and production of defective viral particls (51).

The drug also shows an immunomodulatory effect of the host to the virion as a Th2 response is shifted in favor of a Th1 phenotype. Th2 response and generation of type 2 cytokines stimulate the humoral response that improves the immunity against the virus (29). Ribavirin enhances the induction of genes that synthesis interferon, involving the receptor of interferon-α and down-regulates other genes responsible for apoptosis, interferon suppression, and in vitro hepatic stellate cell activation (52).

Interferon alpha combines with type I interferon receptors (IFNAR2c and IFNAR1), which after dimerization, two Jak (Janus kinase) tyrosine kinases (Tyk2 and Jak1) are activated. These result in transphosphorylation of themselves and phosphorylation of the receptors. After that, the phosphorylated INFAR combine to Stat1 and Stat2 (transcription signal transducers and activators) that dimerize and lead to the activation of numerous (~100) antiviral and immunomodulatory proteins. The binding between type I interferon receptors and interferon alpha is less stable in comparison with interferon beta. (53).

6.5 Evidence / Experience:

- "Used in combination with other antiviral drugs for the treatment of chronic infection of hepatitis C virus (HCV)".(54).
- "The addition of ribavirin is recommended in patients having HCV genotype 1a and 4 infections with or without the presence cirrhosis".(55).
- "Resistance: viral genetic determinants result in variable response to the treatment with ribavirin has not yet determined".(50).
- In the therapy of genital or venereal warts triggered by Human Papiloma Virus.(56).
- Ribavirin is orally administered as it extensively and swiftly absorbed. The administration of 1200 mg ribavirin requires average time of two hours to reach Cmax. A single oral dose of 600mg ribavirin results in bioavailability of 64% 10.(57).
- "The metabolic byproducts of ribavirin are excreted mainly through the kidneys. The excretion of 600mg radiolabeled dose was approximately 61% through the urine and 12% was detected in the feces, While 17% of the dose was secreted in unchanged form 10".(58).

Wide diversities of inducers stimulate vertebrate cells to secrete proteins. They provide resistance to several viral infections, disturb the multiplication of intracellular parasites, and boost natural killer cell activity as well as enhancing granulocyte and macrophage phagocytosis, as well as to several other immunomodulatory effects.(59).

6.6 Safety Concerns:

1. Thrombocytopenia (platelet count is very low).
2. Neutropenia (white blood cells count is below normal level).
3. Vision complications involving retinopathy (retinal damage) that can eventually lead to blindness.
4. Worsening of autoimmune diseases, such as rheumatoid arthritis.
5. Up to date, the drug has been given to more than 127000 infants since it was approved with a considerable safety profile. The noticed adverse reactions involved headaches, nausea and rare worsening of bronchospasms with the beginning of aerosol treatment.(60).

"Neuraminidase suppressors do not appear to be effective against COVID-19 (61). In the case of critically ill patients, Initial empiric treatment with neuraminidase inhibitors is reasonable throughout the period of the influenza season. If the patient is suspected to have influenza pneumonia, nasopharyngeal swabs are taken to test for influenza. Presently, in many situations, patients diagnosed with viral pneumonia is much more likely to be influenza infection rather than COVID-19. The role of the drug especially for COVID-19 is limited". (62).

7. Tocilizumab:

Recommendation: "Recommended against its routine use outside a randomized-controlled trial".

Classification: "Interleukin-6 (IL-6) Receptor-Blocking Monoclonal Antibody".

The reasoning for use: "Severe cases of COVID-19 may suffer from cytokine release". (63).

Mechanism of Action: "The drug competitively binds to IL-6 receptors to suppress interleukin-6 mediated signaling. IL-6 acts as a pro-inflammatory cytokine that has important role in many physiological mechanisms such as the activation of T-cell, stimulation of immunoglobulin secretion, and initiation of hepatic acute-phase protein synthesis, as well as differentiation stimulation and hematopoietic precursor cell division. IL-6 is produced by several cell types, comprising B-cells, monocytes, T-cells lymphocytes and fibroblasts".(64).

- **"Evidence / Experience"**:
- "A retrospective review study evaluated 21 patients in which the drug was added to COVID-19 therapy".(63).
- Preliminary data indicate that the addition of tocilizumab as adjunctive therapy may reveal clinical benefit.
- "Clinical manifestations, including the percentage of lymphocytes, improvements in CT opacity, and C-reactive protein levels in these patients have been improved; however, no comparators were recorded".
- "Several treatment protocols comprise recommendations for use".(41).
- "Additional clinical efficacy data for COVID-19 are being evaluated".(65).

"Safety Concerns": (64).

1. "The risk of gastrointestinal perforation".
2. "The Hepatotoxicity Risk".
3. "Extra caution with cases suffering from neutropenia and thrombocytopenia".
4. "Infusion-related opposite effects".

8. Azithromycin:

"Classification": Macrolide Antibacterial

The reasoning for use: it prevents secondary superinfection by bacteria, macrolides may also have immunomodulatory potential to act as an adjunctive treatment.(46)(66)(67)(68)(69).

Mechanism of Action: "Macrolides may exert immunomodulatory effects in cases with lung inflammation. They can help reduce the excessive release of cytokines by downregulating inflammatory responses associated with viral infections of the respiratory system; however, their direct action on viral clearance is unclear. The

immunomodulatory processes may involve the reduction of chemotaxis of neutrophils (PMNs) to the lungs by the neutralization of cytokines (i.e., IL-8), inhibition of hypersecretion of mucus, decline the production of free radicals, acceleration of neutrophil apoptosis, and suppress the activation of nuclear transcription factors". (66)(67)(68)(69).

"Evidence / Experience":

- "In an open-label, non-randomized clinical trial (n=26); azithromycin and hydroxychloroquine was given as a combination to prevent bacterial superinfection in six patients".(46).
- Preliminary results indicate a possible advantage as an adjunctive therapy.
- "On the sixth day, all of the cases who received the combination (azithromycin and hydroxychloroquine) were completely cured of the virus infection compared with 57.1% of patients who treated with hydroxychloroquine alone (n= 20)".
- "136 patients administered macrolide along with antiviral therapy in a retrospective review of a multicenter cohort study on 349 MERS-CoV cases".(70)
- "Macrolide treatment did not result in a 3-month mortality reduction relative to the control group (adjusted OR: 0.84; 95 per cent CI: 0.47 to 1.51; p = 0.56)".
- "Sensitivity analysis excluding cases who treated with macrolides after three days revealed close results (adjusted OR: 0.7; 95% CI: 0.39 to 1.28; p = 0.25)".

"Safety Concerns": (71) (18).

1. The risk of heart arrhythmia (e.g., QT prolongation).
2. Major drug reactions.

- **Corticosteroids:**

The treatment with corticosteroids is not suggested for viral pneumonia; unless in the case of patients who have a refractory shock or acute respiratory distress syndrome, its use may be considered. (72)(73)(16).

"There are no controlled clinical studies carried on the use of corticosteroids in patients with COVID-19 or other coronaviruses". (74)

"A published, but not peer-reviewed, report about 26 cases having severe COVID-19 indicates that the administration of methylprednisolone at 1-2mg/kg per day for 5 days to one weak was associated with less period of supplemental oxygen use (8.2 days vs. 13.5 days; P) Numerous randomized controlled trials were carried on hospitalized patients with community-acquired pneumonia treated with systemic corticosteroids. A meta-analysis and systematic review of RCTs showed which the need for mechanical ventilation can be reduced by the use of corticosteroids (five RCTs; 1060 patients; RR 0.45, 95% CI 0.26 - 0.79), ARDS (four RCTs; 945 patients; RR 0.24, 95% CI 0.10 - 0.56) and the period of hospitalization (6 RCTs; 1499 patients; MD -1.00 day, 95% CI, -1.79 to -0.21), but elevate the risk of hyperglycemia, which require treatment (75). The disadvantages of these trials are the inclusion of different populations, the outcome on mortality was vague, and the use of different drugs as well as dosing regimens. Furthermore, there are some worries about the use of corticosteroids in viral pneumonia. Thus, the findings may not be applicable to the COVID-19 population".

9. Antibiotic therapy:

Recommendation: To prevent bacterial co-infection, antibiotics should be prescribed on the basis of institutional antibiograms and sensitivities.

Initial Therapy

"As in the case of any viral pneumonia, antibiotics are not benefit to treatment Coronavirus Disease 2019. However, patients showing respiratory symptoms and pulmonary infiltrates on imaging may match the diagnostic criteria for pneumonia. Super infection with pathogenic bacteria is expected, in accordance with the standard therapy of Community-acquired pneumonia (CAP), antibiotics are suggested. An example of a standard treatment of hospitalized patients with CAP is ceftriaxone 1-2g IV per day with intravenous

azithromycin 500mg for three days or oral azithromycin 500mg for a single day followed by 250mg for four days. While cases of COVID-19 who may have contact with travelers or may have a history of travel, rising the spectrum of antibacterial is not necessary unless the patients have significant risk factors for antibiotic-resistant bacteria".

10. NSAIDs

Recommendation: "Paracetamol is recommended especially for the symptomatic treatment of COVID-19 but do not recommend against the use of nonsteroidal anti-inflammatory drugs such as ibuprofen".

"On March 17, The WHO announced that NSAIDs should not be used for the management of COVID-19 symptoms. French officials indicated that the anti-inflammatory medications might exaggerate the infection of the virus based on a recent study published in The Lancet medical journal, which hypothesized that there is an enzyme that can be activated by anti-inflammatory drugs such as ibuprofen and aggravate the infection of COVID-19. After two days, the WHO posted a statement on Twitter declaring that there is no particular reason to avoid the use of NSAIDs according to this data".(72)

Conclusion:

Most of these drugs have been used as trials to treat people infected with the Coronavirus, some of these drugs have had an effect in treating critical cases, such as dexamethasone, and others have been banned from using it.

All of these drugs were used by doctors as experiments because there was no effective treatment or anti-virus vaccines for the Coronavirus, which is why doctors around the world tried to save patients infected with the Coronavirus from death, especially after those infected with the virus reached the stage of artificial respiration

"Recommendations"

1- "Lopinavir / Ritonavir"
   Recommend against the routine use outside of a randomized-controlled trial (RCT) (CATCO).
2- "Remdesivir"
   Because of the limited data on efficacy, the drug is not proposed at this time.
3- "Hydroxychloroquine and Chloroquine"
   Recommend against the routine use outside an RCT.
4- "Oseltamivir"
   Recommend against the use of the drug unless it was assumed or diagnosed to be an influenza infection.
5- "Ribavirin and Interferon":
   Recommend against their use for risk of harm.
6- "Tocilizumab"
   Recommend against the routine use at this time.
7- "Steroids"
   Recommend against the use of steroids.
8- "Antibiotic Therapies"
   If superinfection with pathogenic bacteria is possible, antibiotics should be prescribed according to institutional antibiograms and sensitivities.
9- "NSAIDs/Ibuprofen"
   Paracetamol is recommended particularly for the symptomatic treatment of COVID-19 but do not recommend against the use of nonsteroidal anti-inflammatory drugs such as ibuprofen.

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