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Editorial

Covid-19 and Pharmacologic Treatment

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Abstract

New Coronavirus Disease (COVID-19) is a viral pathology which was first described in Wuhan City of China in late December, as a result of investigations made in a group of patients with respiratory tract symptoms (fever, cough, dyspnea). In 11th February 2020, International Committee on Taxonomy of Viruses (ICTV) declared the name of this new virus as "severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)". This name was chosen due to the relationship of this virus with the coronavirus responsible for 2003 SARS pandemic. Despite this relationship, these two viruses are different [1]. This virus has appeared as a zoonotic virus which mutated to allow human pathogenicity or adapted in a different way [1]. In 30th January 2020, WHO declared COVID-19 as an international public health emergency and a pandemic in 11th March 2020 [1]. An effective treatment is urgently required to treat symptomatic patients, limit the spread of virus in community and decrease viral transport. In this review, the effectiveness of the drugs used in the treatment of Covid-19 and relevance with endocrinologic diseases have been evaluated.

Keywords: *Covid-19; Endocrinology; Treatment*

Diabetes mellitus and COVID-19

Older adults and those with serious chronic medical conditions like heart disease, lung disease and diabetes are at the highest risk for complications of COVID-19 infection. Among mortal COVID-19 cases in Wuhan, China, major associated comorbidities included hypertension (53.8%), diabetes (42.3%), previous heart disease (19.2%) and cerebral infarction (15.4%). People with diabetes who are infected with COVID-19 may experience a deterioration of glycemic control during the illness, like in any other infectious episodes. Metformin, the drug should be discontinued in case of infection as there is a risk of dehydration and lactic acidosis. Sodium-glucose-co-transporter 2 inhibitors; it should be discontinued because there is a risk of dehydration and ketoacidosis during infection. Glucagon-like peptide-1 receptor agonists; patients should be closely monitored for dehydration. Dipeptidyl peptidase-4 inhibitors; since these drugs are generally well tolerated, oral intake can be continued if available. In case of severe systemic infection, insulin therapy should be preferred instead of oral antidiabetics. In addition, hypoglycemic effect of hydroxychloroquine should also be considered [2-4].

Obesity and COVID-19

In some hospitals in Spain, young patients in whom severe obesity was present evolved towards destructive alveolitis with respiratory failure and death (Puig-Domingo M, personal experience). Obesity is associated with sleep-apnea syndrome, as well as with surfactant dysfunction, which may contribute to a worse scenario in case of COVID-19 infection [4].

Adrenal insufficiency

Adrenal insufficiency is a chronic condition characterized with lack of cortisol production. Patients with Addison's disease (primary adrenal insufficiency) and congenital adrenal hyperplasia have a slightly increased overall risk of getting infections. In case of COVID-19 suspicion, corticosteroid dose should at least be doubled to avoid adrenal crisis [4].

Dugs	Mechanism of action	Administration	Contraindications and Adverse Events	Dosing: Renal Impairment: Adult	Dosing: Hepatic Impairment: Adult
Hydroxychloroquine 200 mg tb. [5] (After recent studies, it has been discontinued in some clinics)	Not fully clarified; However, it can change the pH on the cell membrane surface and inhibit viral fusion. It can also inhibit nucleic acid replication, glycosylation of viral proteins, and viral release.	Oral: 400 mg twice daily on day 1, followed by 400 mg/day as a single dose or in 2 divided doses, for a total treatment duration of 5 days Pregnancy: Adverse perinatal outcomes have not been associated with daily maternal doses of hydroxychloroquine ≤400 mg	Contraindications: hypersensitivity Adverse Events: Retinopathy, epithelial keratopathy, exacerbation of porphyria, severe hypoglycemia, weight loss, cardiomyopathy, prolonged QT interval on ECG, torsades de pointes, ventricular arrhythmia, neutropenia, pancytopenia, agitation, confusion, delirium, extrapyramidal reaction, hallucination, deafness, tinnitus, bronchospasm, skin photosensitivity, dyspeptic symptoms	There are no specific dosage adjustments (Use with caution in patients with renal impairment; dosage reduction may be needed)	There are no specific dosage adjustments (Use with caution in patients with hepatic impairment, alcoholism, or concurrent therapy with hepatotoxic agents.)
Favipiravir 200 mg tb. [6]	The mechanism of action is thought to be related to the selective inhibition of viral RNA-dependent RNA polymerase. Other research suggests that favipiravir induces lethal RNA transversion mutations, producing a nonviable viral phenotype.	Oral: Optimal dose and duration unknown, limited data available; 1,600 mg twice daily on day 1, followed by 600 mg twice daily for a total duration of 7 to 14 days Pregnancy: There is evidence that use during pregnancy may result in harm to the baby.	Contraindications: hypersensitivity, pregnancy. Adverse Event: Major adverse reactions included blood uric acid level increase, AST (SGOT) increase, ALT (SGPT) increase, γ-GTP increase, diarrhea, neutrophil count decrease, white blood cell count decrease, blood triglyceride increase, rash, nausea, vomiting, abdominal pain, urinary glucose excretion, blood CK (CPK) increase, hematuria, tonsil polyp, pigmentation, dysgeusia, bruise, blurred vision, ocular pain, vertigo, supraventricular extrasystoles, asthma, oropharyngeal pain, rhinitis, nasopharyngitis, hypokalemia, abdominal discomfort, duodenal ulcer, haematochezia, gastritis, blood ALP increase, blood bilirubin increase	No reductions currently recommended by manufacturer	Yes, with severe hepatic impairment (Child-Pugh class C). When favipiravir was orally administered to subjects with severe liver function impairment (Child-Pugh classification C, 4 subjects) at 800 mg twice daily for 1 day followed by 400 mg twice daily for 2 days (800 mg/400 mg BID), compaired to healthy adult subjects, Cmax and AUC at day 3 were approximately 2.1 fold and 6.3 fold, respectively.

Remdesivir [7]	Inhibition of RNA synthesis	IV: Limited data available; dosing used in clinical trials: 200 mg as a single dose on day 1, followed by 100 mg once daily for a total duration of 5 to 10 days Pregnancy: It is unknown what RDV's impact on pregnancy is, nor do we know if it is excreted in breastmilk. In rats and monkeys, RDV affected kidney development in fetuses.	Contraindications: hypersensitivity, Adverse Events: The most common adverse events were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension.	Measurement of eGFR should be performed while subjects are receiving remdesivir, particularly subjects with known renal impairment at the start of therapy. For subjects with an eGFR of < 30%, permanent discontinuation of remdesivir treatment should be considered.	It is recommended that regular laboratory assessments, including hepatic function tests, be performed in subjects receiving remdesivir in order to monitor hepatic function. For subjects with an ALT > 5 x upper limit of normal (ULN) permanent discontinuation of remdesivir treatment should be considered
Tocilizumab 400 mg [8]	Tocilizumab is an antagonist of interleukin-6 (IL-6) receptor. Endogenous IL-6 is induced by inflammatory stimuli and mediates a variety of immunological responses. Inhibition of IL-6 receptors by tocilizumab leads to a reduction in cytokine and acute phase reactant production.	8 mg/kg (maximum: 800 mg/dose) as a single dose; may repeat dose in 8 to 12 hours if signs/symptoms worsen or do not improve **Or** 4 to 8 mg/kg (usual dose: 400 mg/dose; maximum: 800 mg/dose) as a single dose; may repeat dose in ≥12 hours in patients who remain febrile within 24 hours of initial dose. Pregnancy: At this time, safety and efficacy have not been established and information specific to pregnancy has not been located	Contraindications: hypersensitivity, Adverse Events: Increased serum cholesterol, increased AST and ALT, increased serum bilirubin, hypertension, peripheral edema, skin rash, hypothyroidism, dyspeptic symptoms, leukopenia, neutropenia , thrombocytopenia, nephrolithiasis, headache, conjunctivitis, cough, dyspnea, nasopharyngitis, diverticulitis, active tuberculosis, infection due to an organism in genus Pneumocystis, pneumonia, Herpes zoster reactivation	Baseline ALT or AST >1.5 × ULN is not recommended.	CrCl ≥ 30 mL/minute: No dosage adjustment is necessary. CrCl < 30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); however, based on tocilizumab's molecular weight (148 kDa), it is unlikely to be significantly renally eliminated (expert opinion).

Anakinra 100 mg [9]	Antagonist of interleukin-1 (IL-1) receptor. Endogenous IL-1 is induced by inflammatory stimuli and mediates a variety of immunological responses, including degradation of cartilage (loss of proteoglycans) and stimulation of bone resorption.	SC: It can be administered at doses of 200-600 mg / day depending on the level of cytokine activation. Depending on cytokine activation, treatment can be repeated after 12 or 24 hours. Pregnancy: Information related to the use of anakinra during pregnancy is limited	Contraindications: hypersensitivity, Adverse Events: Headache, vomiting, infection, arthralgia, nasopharyngitis, fever, nausea, diarrhea, eosinophilia, decreased white blood cell count, change in platelet count (decreased), skin rash, increased serum transaminases, metastases (malignant lymphoma, malignant melanoma), hypercholesterolemia	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied).	CrCl ≥30 mL/minute: No dosage adjustment is necessary. CrCl <30 mL/minute or end-stage renal disease (ESRD): Consider administering the prescribed dose every other day. Hemodialysis: Not dialyzable (<2.5%). Continuous ambulatory peritoneal dialysis (CAPD): Not dialyzable (<2.5%)
Anticoagulation [10] - Low molecular weight heparin - Unfractionated heparin - Fondaparinux (used in history of immune mediated heparin-induced thrombocytopenia (HIT))	Routine test: -Complete blood count (CBC) including platelet count -Coagulation studies (prothrombin time [PT] and activated partial thromboplastin time [aPTT]) -Fibrinogen -D-dimer Participation in clinical trials is encouraged in order to improve understanding of the most effective and safest means of preventing and treating thrombotic complications of COVID-19. Heparin acts as an anticoagulant by enhancing the inhibition rate of clotting proteases by antithrombin III impairing normal hemostasis and inhibition of factor Xa. Low molecular weight heparins have a small effect on the activated partial thromboplastin time and strongly inhibit factor Xa.	**Prophylactic** Enoxaparin –40 mg once daily; BMI >50 kg/m2: 60 mg every 12 hours -Dalteparin – 5000 units once daily. -Nadroparin – For patients ≤70 kg, 3800 or 4000 anti-factor Xa units once daily; for patients >70 kg, 5700 units once daily. In some cases, doses up to 50 anti-factor Xa units/kg every 12 hours are used. -Tinzaparin – 4500 anti-factor Xa units once daily. -For patients with CrCl <15 mL/min or renal replacement therapy, we use unfractionated heparin. 5000 units SC every 12 hours. **Therapeutic** Enoxaparin 1 mg/kg SC every 12 hours Dalteparin 100 units/kg SC every 12 hours Unfractionated heparin: continuous IV infusion or a SC dose every 12 hours. Titrated to keep the aPTT in the therapeutic range.	Contraindications: hypersensitivity, history of immune mediated heparin-induced thrombocytopenia (HIT) in the past 100 days or in the presence of circulating antibodies; active major bleeding; acute or subacute bacterial endocarditis; major blood clotting disorders; active gastric or duodenal ulcer; hemorrhagic cerebrovascular accident (except if there are systemic emboli); severe uncontrolled hypertension; diabetic or hemorrhagic retinopathy **Adverse Reactions** Anemia, hemorrhage, peripheral edema, confusion, nausea, ecchymoses, thrombocytopenia, increased serum ALT and serum AST, hematoma, hematuria, fever	**Prophylactic** -Enoxaparin-For patients with creatinine clearance (CrCl) >30 mL/min, 40 mg once daily for CrCl 15 to 30 mL/min, 30 mg once daily. -Dalteparin – CrCl <30 mL/min: Use an anticoagulant with less dependence on renal clearance. -Nadroparin -CrCl <30 mL/min: Contraindicated -Tinzaparin –CrCl <30 mL/min: Use with caution, although evidence suggests no accumulation with CrCl as low as 20 mL/min **Therapeutic** Enoxaparin -CrCl ≥ 30 mL/min: No adjustment, CrCl < 30 mL/min: Reduce to 1 mg/kg once daily	There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); use with caution

Dexamethasone [11] (Hospitalized patients who require mechanical ventilation or supplemental oxygen (IDSA [Bhimraj 2020]; NIH 2020; RECOVERY 2020).	Dexamethasone is a long-acting corticosteroid with the limited potential for sodium retention. It decreases inflammation by suppressing neutrophil migration, decreasing inflammatory mediator output, and suppresses normal immune response.	IV, Oral: 6 mg once daily for up to 10 days (or until discharge if sooner); equivalent glucocorticoid dose may be substituted if dexamethasone is unavailable (Hornby 2020; IDSA [Bhimraj 2020]).	Hypersensitivity, systemic fungal infections	There are no dosage adjustments provided in the manufacturer's labeling.	There are no dosage adjustments provided in the manufacturer's labeling.
COVID-19 Immune (Convalescent) Plasma [12,13]	CT findings are consistent with COVID-19 and > 50% increase in lung infiltration within 24 - 48 hours, respiratory rate> 30/ minute, PaO_2 / FiO_2 <300 mm Hg, Oxygen saturation < 90% despite nasal oxygen support of 5 liters/minute and above, Partial oxygen pressure < 70 mm Hg, despite nasal oxygen support of 5 liters/minute and above, If there is a need for mechanical ventilation, An increase of at least 2 points in the SOFA score, If there is a need for a vasopressor in severe hypotension, Severe lymphopenia Severe CRP, ESH, ferritin, LDH and D-dimer elevation.	The minimum recommended dose for a patient is 1 daily from a 200 milliliter COVID-19 immune plasma unit, and a maximum of 3 doses (600 milliliters) with an interval of 48 hours if necessary.	IgA deficiency, It is not recommended for use during the cytokine storm period, transfusion reactions	-	-

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