Immunosuppressant Drugs Therapy with COVID-19: Associated Risks, Drug-Drug Interactions & Contraindications

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Abstract

Immunosuppressant drugs like Etanercept, Mycophenolate mofetil, Sirolimus, Cyclosporine and Rituximab can weaken the immune system and make patients susceptible to SARS nCoV-2 virus. These drugs make immunocompromised persons more vulnerable to complications associated with COVID-19. Moreover, it can also increase the mortality and morbidity, as a weakened immune system can lead to longer duration of infection. This study discusses the guidelines on immunosuppressant drugs and its associated risk factors with COVID-19, issued by the U.S CDC (Centers for Disease Control and Prevention), WHO (World Health Organisation), U.S FDA (Food and Drug Administration) and other accredited global health organisations. Moreover, it also includes information about pharmaceutical properties, mechanism of action, COVID-19 associated risk factors, adverse drug reactions, contraindications and drug-drug interactions. Our study will help government partners and international health organisations to better understand COVID-19 health risks associated with immunosuppressants. Increased public awareness about effective drug therapy for autoimmune diseases, cancer treatment, immunocompromised and organ transplant patients will help lower the mortality and morbidity associated with the disease amid COVID-19 pandemic.

1. INTRODUCTION

As per the U.S Department of Health and Human Services and U.S FDA, immunosuppressant drugs can cause susceptibility to viruses leading to infection with increase in morbidity of the disease. It can cause severe risk of illness from COVID-19 due to a weakened immune system. Immunosuppressant drugs like Etanercept, Mycophenolate mofetil, Sirolimus, Cyclosporine and Rituximab can weaken the immune system and make patients vulnerable to COVID-19 [1-2]. These drugs suppress the body's immune response to prevent organ rejection during solid organ transplantation and could be used to treat autoimmune disorder, Crohn's disease, Rheumatoid arthritis, Psoriasis, Nephrotic syndrome, and lung disease like lymphangioleiomyomatosis. Immunosuppressants can lower the body's defence mechanism to ward off viruses and infections. However, it is recommended not to stop immunosuppressants without consulting respective healthcare providers as it can lead to flare up of the underlying disease or treatment process. Immunosuppressants can be stopped temporarily if someone is not feeling well and develops fever, sore throat, runny nose or any other respiratory symptoms. It can be continued again once a person feels better [3-5].

COVID-19 precautionary measures are advised for immunocompromised patients suffering from underlying medical conditions like cancer, HIV, genetic immune deficiencies, multiple sclerosis, lupus, rheumatoid arthritis. Patients undergoing treatment procedures like bone marrow transplant, solid organ transplant, stem cells transplant are also advised to follow the same guidelines as advised by the U.S CDC. Also, patients taking immunosuppressant drugs like etanercept, mycophenolate mofetil, sirolimus, cyclosporine and rituximab irrespective of their medical condition should maintain enhanced COVID-19 precautionary measures like refrain from non-essential travel, avoid touching eyes and mouth with unwashed hands, wear N95 respirator or cloth mask, maintain social distancing of at least 6 feet and stay at home as much as possible.

Moreover, they should disinfect household objects touched frequently and avoid sharing personal items with others, wash hands with soap and water for at least 20 seconds or use hand sanitizer with at least 60% alcohol content. In this study, we discuss the pharmaceutical properties of immunosuppressant drugs, associated risk factors with COVID-19, contraindications, adverse reactions and drug-drug interactions [6-9].

2. METHODOLOGY

In this review, online literature search was done on Medline, PubMed and google scholar databases for studies on hospital-based management/ treatment of COVID-19 globally and relevant studies were identified. This review includes various immunosuppressant drugs therapy and their effect on COVID-19 patients . The drugs such as Etanercept, Mycophenolate mofetil, Sirolimus, Cyclosporine and Rituximab are described in detail. The review describes the drug pharmaceutical properties, mechanism of action, risk associated with the drug therapy for COVID-19, contraindications, drug-drug interactions, side effects and risks.

Etanercept

Pharmaceutical Properties

Enbrel is the brand name of Etanercept which has a wide range of usage in terms of reducing signs and symptoms for polyarticular juvenile idiopathic arthritis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis etc. Enbrel can be presented in the form of a 25mg multiple use vial which appears as a white sterile lyophilized powder containing inactive ingredients like 10mg sucrose, 40mg mannitol and 1.2mg tromethamine with pH varying from 7.1 to 7.7. It can also be presented as a 25mg/50mg prefilled syringe which contains inactive ingredients like 25mM L-arginine hydrochloride, sodium phosphate, 1% sucrose and 100mM sodium chloride. It appears clear, colorless and sterile with pH varying from 6.1 to 6.5. Enbrel is linked to the Fc (fragment crystallizable) portion of human IgG1 (immunoglobulin G) through the tumor necrosis factor receptor (TNFR). Enbrel is a dimeric fusion protein which consists of a human 75 kilodalton (p75) extracellular ligand binding portion [10-12].

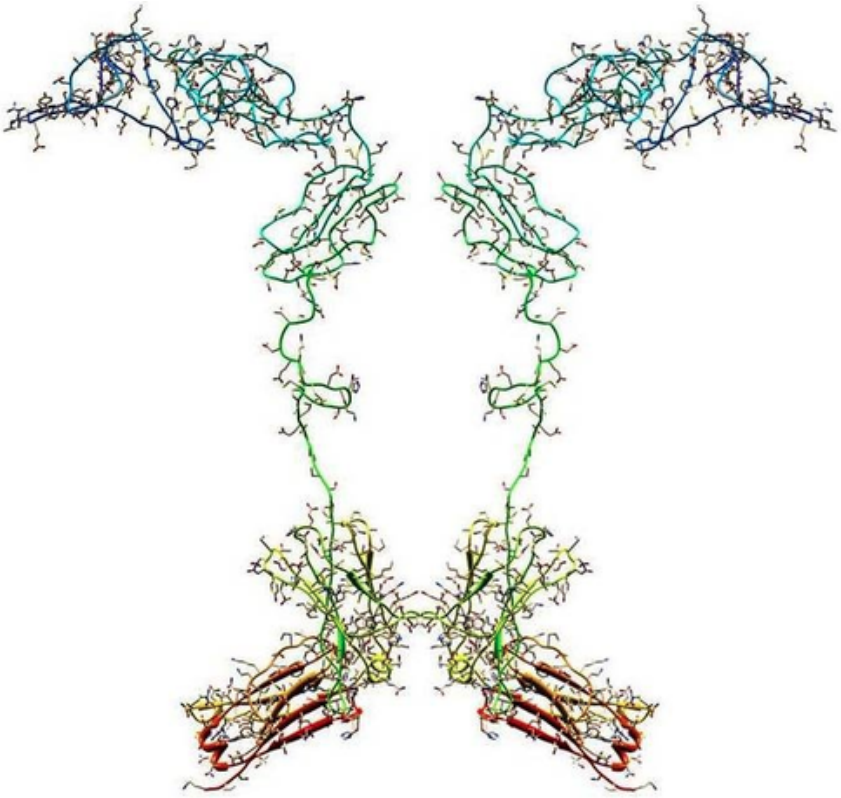

Figure 1: Protein Structure of Etanercept

Mechanism of Action

Enbrel can bind to tumor necrosis factor (TNF) molecules in dimeric soluble form. It is involved in immune and inflammatory responses as it is a cytokine and it inhibits binding of TNF-alpha and TNF-beta on the cell surface leading to inactivation of tumor necrosis factor (TNF). It plays a crucial role in the inflammatory process response of joint pathology [13].

Risks Associated with Etanercept and COVID-19

Enbrel or Etanercept if taken concomitantly with other immunosuppressants like Methotrexate or corticosteroids, can cause hospitalization or mortality through serious infections. It is recommended that if serious infection or sepsis develops then Enbrel should be discontinued [11]. Some of the infections reported are associated with viral, bacterial and fungal infections. It can also cause active tuberculosis or reactivation of latent tuberculosis. Fungal infections like candidiasis, aspergillosis, coccidioidomycosis, histoplasmosis\sout, etc. are associated with Enbrel. As per American College of Rheumatology (ACR) and British Society of Rheumatology, patients with ongoing treatment with Etanercept are considered high risk for COVID-19. CDC guidelines should be followed to protect patients from active infections. It is also recommended that patients should continue their treatment plan unless there is evidence of active infection. Moreover, stopping medication abruptly or altering treatment dose plan is not recommended as it can exacerbate the disease [14].

Drug-Drug Interactions, Adverse Reactions & Contraindications

Enbrel is not recommended for patients taking cyclophosphamide, especially for those suffering from Wegener granulomatosis as it can cause a higher incidence of solid malignancies. Similarly, Enbrel is not recommended

with Sulfasalazine as it can lead to reduction of neutrophil count. Enbrel should be given to patients with live vaccines specifically varicella viruses, but it can be considered for prophylactic treatment as well. Based on clinical trials, Enbrel can cause adverse reactions for patients with plaque psoriasis, ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, etc. [13]. In terms of contraindication, Enbrel should not be administered to patients with sepsis.

Mycophenolate Mofetil

Pharmaceutical Properties

Mycophenolate mofetil (MMF) is an immunosuppressive drug with chemical name 2-morpholinoethyl (E)-6-(1,3-dihydro-4hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate and chemical formula - $C_{23}H_{31}O_7$. It physically appears as a white crystalline powder with increased solubility in acidic medium at pH 3.6. It can be consumed orally with tablets present in the form of 250mg and 500mg. Some of the inactive ingredients present in a 250mg and 500mg mycophenolate mofetil tablet are magnesium stearate, sodium, pregelatinized starch, etc. [15-16].

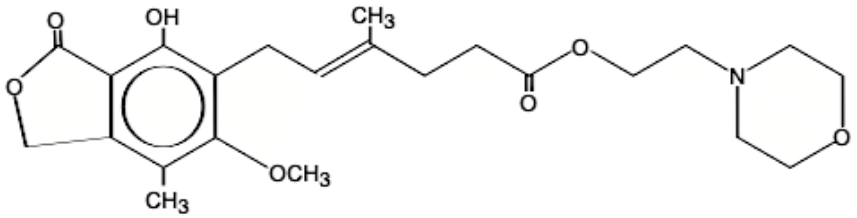

Figure 2: 2D Chemical Structure of Mycophenolate mofetil

Mechanism of Action

Mycophenolate mofetil (MMF) upon oral administration is hydrolyzed to mycophenolic acid (MPA) which is an active metabolite. It incorporates into the DNA and blocks the *de novo* pathway of guanosine nucleotide synthesis and reversibly inhibits inosine monophosphate dehydrogenase (IMPDH). It inhibits the proliferation of B and T lymphocytes as they are dependent upon the *de novo* synthesis of the purines [15, 17].

Risks associated with Mycophenolate Mofetil and COVID-19

Immunosuppressive drugs like MMF can lead to increased susceptibility of patients to infections. Patients taking MMF as part of their treatment plan are considered high risk and advised to undertake increased precautionary measures against COVID-19. Renal, cardiac and hepatic transplant patients taking MMF are considered vulnerable and should be managed with facilities staffed with adequate resources with support therapy and treatment to reduce mortality associated with COVID-19. Moreover, it can also lead to development of lymphoma in solid organ transplant patients [18-19].

Drug-Drug Interactions, Adverse Reactions & Contraindications

As per the U.S FDA, the antacid Maalox TC (magnesium and aluminium hydroxide) when taken concomitantly reduces the absorption of Mycophenolate Mofetil. it also reduces the area under the curve (AUC). Moreover, a variation of the drug concentration in blood plasma over a period of time also reduces the maximum serum concentration of the drug (C_{max}). All the above conditions are compared when MMF is taken orally while fasting. In addition, persons who use MMF are at increased risk of infections, including progressive multifocal leukoencephalitis (PML) and opportunistic infection among renal, cardiac and hepatic transplant patients. The use of MMF is contraindicated during pregnancy as it can cause congenital malformations and miscarriages [15].

Sirolimus

Pharmaceutical Properties

The Immunosuppressant drug Sirolimus also known as Rapamune,is a macrolide antiobiotic. The molecular formula of Sirolimus is $C_{51}H_{79}NO_{13}$. Physically, it is off white in color in powdered form. It is soluble in solvents such as acetone, acetonitrile, chloroform, benzyl alcohol, \soutetc. and is also insoluble in water. The inactive ingredients in Rapamune oral solution are ethanol, mono and diglycerides, ascorbyl palmitate, propylene glycol, phosphatidylcholine etc. Some of the inactive ingredients for Rapamune tablets are microcrystalline cellulose and include talc, titanium dioxide, lactose, sucrose, polyethylene glycol, calcium sulphate, and magnesium stearate [20-21].

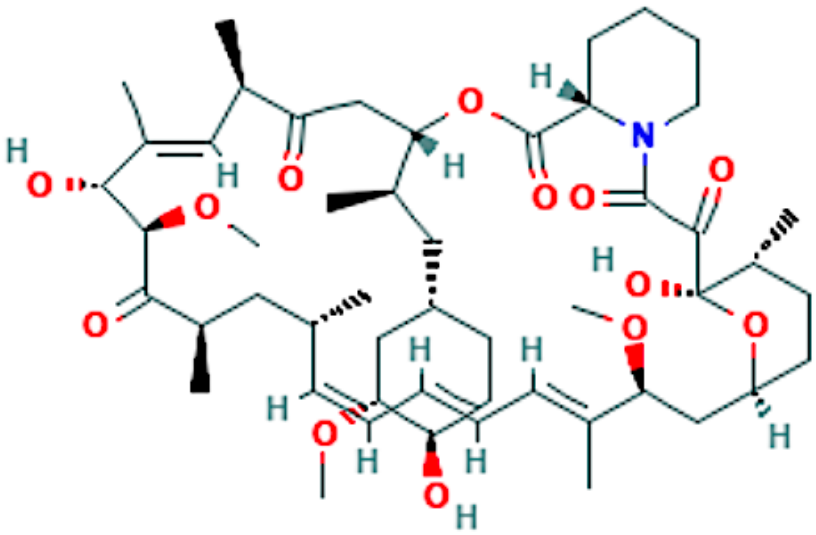

Figure 3: 2D Chemical Structure Sirolimus

Mechanism of Action

Sirolimus stimulates cytokines like IL-2 (interleukin-2), IL-4, IL-15 and inhibits proliferation and activation of T-lymphocytes. It binds to FK binding protein 12 (FKBP12), immunophilin to generate an immunosuppressive complex. It has no effect on calcineurin activity and it inhibits the activation of a key regulatory kinase - mTOR (mammalian target of rapamycin) [20].

Risks associated with Sirolimus and COVID-19

Sirolimus is efficient for immunosuppression in transplant patients where it acts prophylactically especially in renal transplant. It increases susceptibility to infection due to which patients are at high risk for COVID-19. It can cause complications like lowering of lung function like FEV1 (forced expiratory volume). It is important to follow CDC guidelines as recommended. Moreover, it is also advised that LAM (lymphangioleiomyomatosis) patients who suffer from abnormal growth of muscle like cells in lungs, lymph nodes or kidneys are at high risk of contracting COVID-19 due to intake of Sirolimus. But, due to the nature of their illness, it is advisable that they continue with their treatment plan. It is important for the healthcare provider to decide upon dose reduction or treatment interruption in certain circumstances wherein patients are at high risk of COVID-19 transmission [22].

Drug-Drug Interactions, Adverse Reactions & Contraindications

In terms of drug-drug interactions, concentration of Sirolimus can increase with concomitant use of CYP3A4/P-gp inducers or inhibitors. Verapamil can also increase the concentration of Sirolimus while

drugs like Phenobarbital, Rifapentine, St. John Wort (*Hypericum perforatum*), Carbamazepine can decrease the concentration of Sirolimus. Certain other drugs like diltiazem, fluconazole, cimetidine, bromocriptine, protease inhibitors like ritonavir, indinavir and telaprevir\sout, etc. can increase blood concentration of Sirolimus [20]. The use of Sirolimus is not recommended for liver transplant patients as it can cause high mortality due to hepatic artery thrombosis and graft loss,while it can cause bronchial anastomotic dehiscence in lung transplant patients. Most commonly, it can cause peripheral edema, hypertension, hypercholesterolemia in patients with renal transplant. It is contraindicated for patients suffering with hypersensitivity which includes symptoms like anaphylactic reactions, angioedema, hypersensitivity vasculitis, exfoliative dermatitis. [23].

Cyclosporine

Pharmaceutical Properties

Cyclosporine is an immunosuppressive drug which has shown remarkable success in kidney, liver, heart allogeneic transplant. It suppresses humoral immunity to a greater extent along with delayed hypersensitivity, allograft rejection due to cell mediation and allergic encephalopathy. \soutAs per the U.S FDA, It is reported that 90% of cyclosporine is bound to lipoprotein in blood, but largely it is distributed outside the blood volume. The uptake of cyclosporine are as follows : erythrocytes (41-58%), plasma (33-47%), granulocytes (5-12%) and lymphocytes (4-9%), while in leukocytes and erythrocytes, it saturates at higher concentrations [24-25].

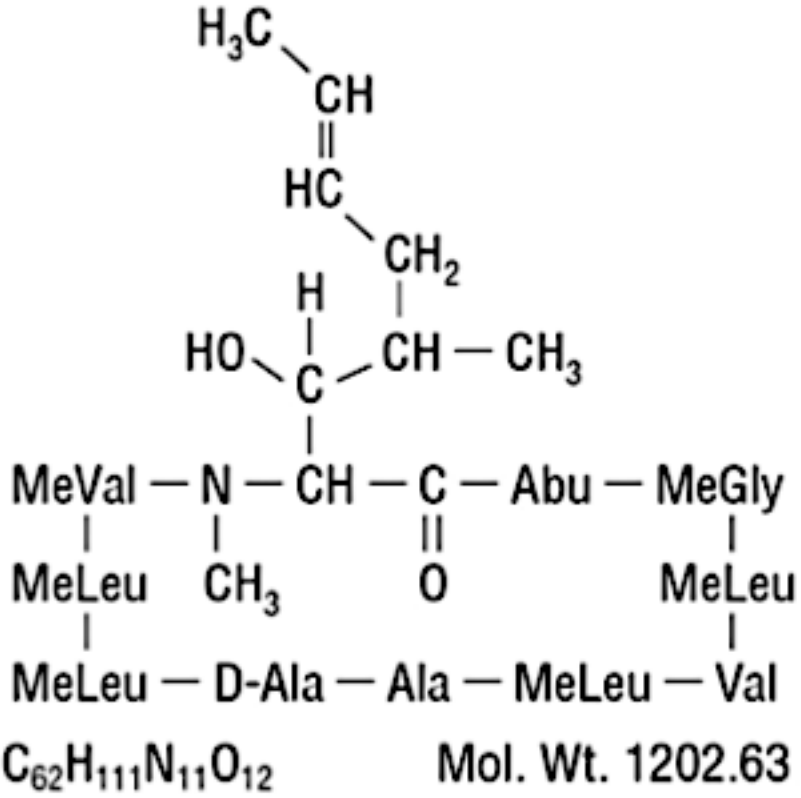

Figure 4: 2D Molecular Structure of Cyclosporine

Mechanism of Action

Cyclosporine reversibly inhibits specific lymphocytes in the G0 and G1 phase of cell cycle. T-helper and T-suppressor cells are suppressed. It releases T-cell growth factor (TCGF) or interleukin-2 and inhibits T-lymphocytes and lymphokine production [24].

Risks associated with Cyclosporine and COVID-19

Cyclosporine is part of immunosuppressive therapy. It is advised to administer Cyclosporine with corticosteroids in organ transplant patients. It increases risk for infection and lymphoma formation. Due to the current COVID-19 pandemic, it is advised to significantly reduce the dose of certain immunosuppressive agents wherein patients who are heart, liver or kidney transplant recipients are exposed to the virus. For outpatients, they can continue the dose as recommended to avoid frequent visits to the doctor [26-27].

Drug-Drug Interactions, Adverse Reactions & Contraindications

Cyclosporine can increase plasma concentration of comedications which are substrates of CYP3A4 as it is an inhibitor of CYP3A4. It can also lead to reduced clearance of drugs like sirolimus, aliskiren, HMG CoA reductase inhibitors like statin, digoxin, colchicine, prednisolone, etoposide, etc. It is important that drug-drug interactions are reviewed prior to administering cyclosporine with any other pharmaceutical drugs as higher concentration of cyclosporine can cause nephrotoxicity and hepatotoxicity. Importantly, nephrotoxicity is noted among cardiac transplant patients (38%), liver transplant patients (37%) and renal transplant patients (25%). Moreover, it can also lead to rising levels of BUN (blood urea nitrogen) and creatinine. Cyclosporine is contraindicated among patients suffering from hypersensitivity to cyclosporine and polyoxyethylated castor oil [24, 28].

Rituximab

Pharmaceutical Properties

Rituximab is also known as Rituxan (brand name). It is directed against CD20 antigen as it is a genetically engineered IgG1 monoclonal kappa antibody. It contains the antibiotic gentamicin and is produced by mammalian cells in a nutrient medium using suspension culture. It can be administered intravenously and it appears as a clear colorless sterile, preservative free liquid concentration available as 100mg/10ml or 500mg/50ml vials. The pH of Rituximab is 7.4 and formulated using sodium citrate dihydrate, sodium chloride, polysorbate 80 and water for injecting purposes [29-31].

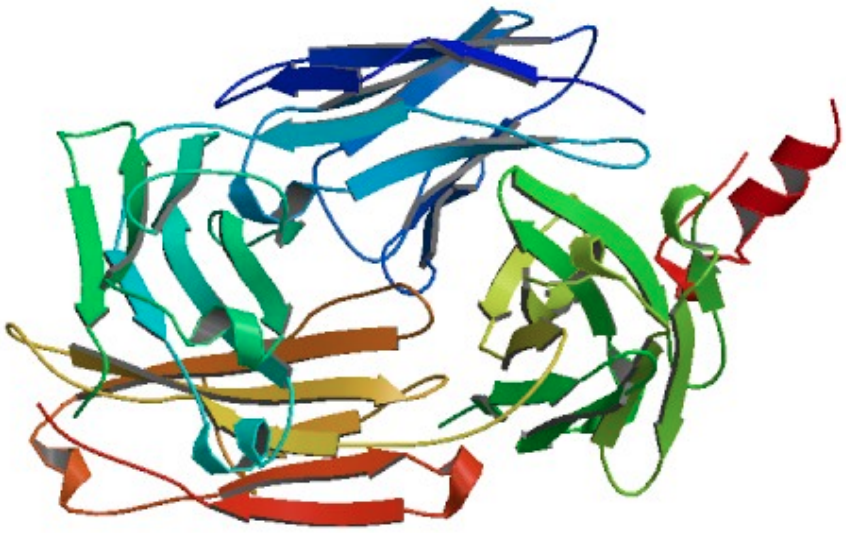

Figure 5: Protein Structure of Rituximab

Mechanism of Action

Rituximab binds to CD20 antigen on B lymphocytes through Fab domain. B cell lysis in-vitro occurs through immune effector functions which are recruited by Fc domain. It involves certain mechanisms like ADCC (antibody dependent cell mediated cytotoxicity) and CDC (complement dependent cytotoxicity). It can induce apoptosis to the DHL-4 (diffuse histiocytic lymphoma) human B-cell lymphoma line [29].

Risks associated with Rituximab and COVID-19

Rituximab can cause fatal infusion reactions with tumor lysis syndrome, progressive multifocal leukoencephalopathy, severe mucocutaneous reactions with high mortality rate. Moreover, in-patients taking rituximab are at high risk with complications associated with COVID-19. It makes patients more susceptible to contract COVID-19 with symptoms like fever, cough, myalgia leading to respiratory failure requiring endotracheal intubation and mechanical ventilation. It's quite important to follow U.S CDC guidelines to protect patients from life threatening complications of COVID-19 as Rituximab can deplete B-cells which secretes antibodies in adaptive immunity and functions in humoral immunity [31-32].

Drug-Drug Interactions, Adverse Reactions & Contraindications

Rituximab can cause renal toxicity with cisplatin. Toxicity associated with patients of Non-Hodgkin lymphoma (NHL) are more susceptible. It can cause fatal toxicity if patients experiencing tumor lysis syndrome are administered Rituximab concomitantly with Cisplatin. They can show signs of renal failure with rising serum creatinine level or oliguria. Rituximab with Cisplatin is not approved concomitantly. Rituximab can cause lymphoid malignancy leading to infusion reactions, fever, lymphopenia, infection, asthenia - physical weakness and lack of energy, neutropenia, etc. As per U.S FDA, it doesn't have any contraindications but it can cause common adverse reactions like upper respiratory infection, bronchitis, nasopharyngitis, urinary tract infection, etc. in patients with rheumatoid arthritis. Moreover, it can cause muscle spasm, peripheral edema, diarrhea, nausea, etc. in patients suffering with microscopic polyangiitis (MPA) and Wegener's granulomatosis or granulomatosis with polyangiitis (GPA) [29, 33-34].

Table 1: Immunosuppressant Drugs Therapies with COVID-19: Associated Risks, Adverse Reactions and Drug-Drug Interactions

Immunosuppressant Drugs	Associated Risks with COVID-19
Etanercept	Infectious complications in patients suffering with rheumatoid and immune diseases. Follo
Mycophenolate Mofetil	Oversuppression of the immune system can give rise to infections and make immunocompr
Sirolimus	Patients taking immunosuppressant drugs are more susceptible to COVID-19 specifically t
Cyclosporine	COVID-19 in-vitro studies show inhibition of the replication of the coronaviruses as cyclos
Rituximab	It can deplete lymphocytes leading to serious complications associated with COVID-19. It

DISCUSSION

Our study discusses the role of immunosuppressant drugs and susceptibility to SARS nCoV-2 virus along with its associated risk factors, adverse reactions, drug-drug interactions and contraindications. The study conducted by Brownstone ND, Thibodeaux QG, Reddy VD et. al., 2020 and Zhang C, Wu Z, Li JW et. al., 2020 shows Etanercept can cause serious COVID-19 infection risk for patients undergoing treatment for psoriasis leading to upper respiratory infection, influenza and serious infections. Moreover, patients who are older with comorbid conditions like lung disease, hypertension, diabetes, cancer or taking immunosuppressive drugs, etc. are also at serious risk of developing infection [35-36]. Another study by Del Papa N, Sambataro G, Minniti A, Pignataro F et. al., 2020 shows the role of mycophenolate mofetil's in suppression of immune system of systemic sclerosis (SSc) leading to heightened vulnerability to develop COVID-19 with worse clinical outcomes. Chronic immunosuppressive therapies with SSc need to maintain precautions amid COVID-19 pandemic. It is associated with increased morbidity and mortality specially with underlying medical

conditions like primary cardiomyopathy and secondary to pulmonary hypertension [37]. Zhou Y, Hou Y, Shen J, Huang Y et. al., 2020 shows that clinical application of Sirolimus reduces MERS (Middle East Respiratory Syndrome) CoV infection. It is also used to manage patients with acute respiratory failure and severe H1N1 pneumonia. The study also discusses the role of Sirolimus in autoimmune diseases including systemic lupus erythematosus, Crohn's disease, rheumatoid arthritis, etc. [38]. de Wilde AH, Zevenhoven-Dobbe JC, van der Meer Y et. al., shows Cyclosporin's effect on the replication of severe acute respiratory syndrome coronavirus (SARS-CoV). The study states that the mechanism of inhibition remains to be established. It reports that it is associated with one or multiple members of the cyclophilin family and it interferes with the functional interactions of viral proteins [39]. Another study by Willis MD, Robertson NP et. al., 2020 shows increased risk of infection among vulnerable cohort study populations suffering from multiple sclerosis. It also shows a serious risk of infection with Rituximab amid COVID-19 pandemic [40]. Overall, patients are advised to continue with their immunosuppressant medications unless they are asked by their respective healthcare provider to reduce the dosage or halt medication temporarily based upon the patient's current condition and risk of contracting COVID-19.

CONCLUSION

Patients taking immunosuppressant drugs are susceptible to COVID-19. Immunosuppressant drugs like etanercept, mycophenolate mofetil, sirolimus, cyclosporine and rituximab are prescribed for several reasons such as autoimmune disease, cancer treatment, organ transplant, etc. It is recommended that patients should continue with their treatment regime in the midst of COVID-19 pandemic. Any changes pertaining to immunosuppressant drugs like reducing dosage or halting medications temporarily should be discussed with concerned healthcare providers. Patients need to be aware of CDC guidelines on ways to prevent exposure to the SARS nCoV-2 virus.

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AUTHORS' CONTRIBUTIONS :

DT: Concept, Data Collection, Writing & Review the manuscript, Design

MMG: Concept, Data Collection, Writing & Review the manuscript, Design

DI**:** Writing & Review the manuscript

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