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Immunology and Immunotherapy of COVID-19: A Review

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ABSTRACT

Coronavirus disease 2019 is caused by severe acute respiratory syndrome coronavirus 2(SARS-COV-2). The virus was initially named "2019-nCOV" but later on SARS-COV-2 name is given by the coronavirus study group of International committee on taxonomy of viruses (ICTV).On 30 January 2020 World Health organisation declared as a global health emergency and on 11 March 2020 COVID-19 disease as a pandemic. Understanding the human effects of COVID-19 can pave the way for a rational choice of the appropriate Immunotherapy. Still there is a need to study more about the immune system, how immune system play important role on disease severity and mortality rate? During disease progression a change occurs in human responses is suggested by initial study so poor ability of host immune responses might be one of the important factors for pathogenesis and disease severity of COVID-19. There is urgent need to control this COVID-19 disease. In this review we summarise the Clinical Signs & Symptoms, Immunopathogenesis, innate and adaptive immune responses against virus as well as immunotherapeutic potential that will help to inhibit COVID-19 infection based on recently identified data on SARS – COV-2.

Keywords: COVID-19, SARS COV-2, Immunopathogenesi Innate & Adaptive Immunity, Clinical Signs & Symptoms, Immunotherapies

Introduction:

A type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only target certain cells of the immune system. The SARS- COV-2 consists of crown like spike on external surface is called coronavirus. In Wuhan, Hubei province China the outbreak of coronavirus 2019 started, in December 2019 pneumonia case was reported but infectious agent is not known in origin . SARS-COV-2 is the seventh member of coronavirus family which are envelope the positive single stranded RNA and genus beta coronavirus which is same for SARS-COV-1 ,MERSSubfamily of SARS-COV-2 .Coronavirinae has a four genera such as Alpha (α)Beta (β)Gamma(γ) and Delta(δ) coronavirus, origin of this for general as alpha and beta from mammals (Bat) and Gamma, Delta from birds and pigs.

SARS-COV-2 enter into the host cell with the help of host cell receptor Angiotensin converting enzyme 2(ACE-2) by interact with spike (S) protein and putative ligand which majorly found on epithelial cells of lungs hence in COVID-19 disease lungs are affected primarly ,The genome of SARS-COV-2 consists of 14 open reading frames Human coronaviruses were 229 E,OC43,NLG3 and HKU1 which cause mild to moderate cold or flu like symptoms while animal viruses are SARS-COV-1,MERS and SARS-COV-2 but the transmission rate of SARS-COV-2as compared to other two viruses is higher.

The severe acute respiratory syndrome coronavirus 2 (SARS -COV-2) can cause attack to all age groups but high mortality rate is seen in a high aging groups with underlying conditions like hypertension diabetes and in people with poor immune activity, another study showed that 5% of patients require intensive Care support and over 20% of critical cases succumb to Severe disease. There are no appropriate vaccines for antiviral therapy to protect or treat against COVID-19 hence once infected case management is entirely supportive care.

Clinical signs and symptoms of COVID-19

SARS-COV-2 is mainly transmitted through close contact by respiratory droplets of the infected patients as well as contact with infected surface has also been suggested, most covid-19 patients exhibit symptoms approximately after 5.2 days .According to the severity of symptoms patients can be classified as mild, severe, and critical. The most commonly reported symptoms are fever, dry cough, myalgia, fatigue, headache and dyspnea, loss of smell and taste , diarrhoea haemoptysis and runny nose and Stroke. Most critically ill patients include respiratory failure which can result in lethal pneumonia covid-19 can cause gastrointestinal tract symptoms which are not found in MERS and SARS COV1.

Recent studies have reported an incidence between 3 to 9% of acute kidney injury in covid-19 patient, cardiovascular complications including myocardial injury and myocardial acute myocardial infarction, heart failure and venous thromboembolic other symptoms is intestinal pain. Regarding a colour tissue some studies have also identified the manifestation of conjunctivitis in patients with covid-19. Recently reports on covid-19 found that the occurrence of coagulation abnormality in most critically ill patients.

Immunopathogenesisof COVID -19:

After entry, the first location that virus starts to replicate is the airway epithelial cells. Virus starts its infection by burning the viral particle to the host cellular receptors. The humans SARS- COV 2genome consists the 5'-untranslated region (5'-UTR) open reading frame (ORF) that encodes the structural proteins including spike (s) Envelope (E) Membrane (M)Nucleocapsid(N) ORFs 3,6,7a,7b,8 and 9b encoding accessory proteins and 3' UTR. E protein helps in virus assembly protein has three trans membrane domains and shapes.N protein content to do means which helps in RNA synthesis .The highest protein consists of two subunits S1 and S2 specially n-terminal S1 subunit play important role in binding the host cell receptor (ACE2) angiotensin converting enzyme 2 Transmembrane Serine protease 2(TMPRSS2) cleaves virals glycoprotein through endosomal pathway to facilitate viral activation . The incubation period of SARS-COV-2 was 3 to 7 days and approximately 80% of infections are mild or asymptomatic,15% are severe, requiring oxygen and 5% are critical infections requiring ventilation . ACE2 present in plasma membrane mainly of pulmonary, endothelial cardiac and renal.S2 subunit is known to contain the fusion peptide in which it is inserted into host cell membrane the binding of the virus to the ACE2 receptor causes stabilization of RBD in standing upstate and trigger conformational changes in s complex. As covid-19 can enter the small intestine and upper respiratory tract cell cause upper respiratory and gastrointestinal symptoms. IN SARS COV2 infection the expression of the ACE2 receptor by the lungs cells has reported being decreased therefore ACE-2 downregulation in lungs cells is another pathologic mechanism of SARS-COV leading to acute lung injury and acute respiratory distress syndrome (ARDS). A study indicated that adipose tissue expresses the ACE2 receptor adipose cells can be infected with SARS-COV-2. Alveolar macrophages exert and inflammatory immune response against the virus by producing proinflammatory cytokines and chemokines such as interferon-gamma,IP10, monocyte, tumor necrosis factor,interleukin The release of this proinflammatory cytokines and chemokines to the blood stimulates and inflammatory response in the lung by recreating blood monocytes and T lymphocytes The inflammatory response can vary from mild inflammation to severe in inflammation. Severe pulmonary inflammation also increases capillary that can cause ARDS thus the immune response against SARS-COV-2 and the severity of the inflammation are two major factors that define the outcomes in patients with covid-19 . In recent study Zhao et al. Inspected the relationship between the ABO blood group and covid-19 infection this study demonstrated that individuals with A blood group were at an in the increased risk for covid-19 while O blood group individual had a reduced risk for covid-19 infection the lower susceptibility of O blood group patient can be explained by the presence of the cross neutralizing antibody and group antibodies against SARS-COV-2 in their serum this anti blood group antibodies and especially anti -A antibodies have shown neutralizing activity against the SARS-COV-2and can thus reduce the risk of infection with SARS-COV -2 in patients with O blood group . Studies have demonstrated that the lymphopenia mostly results from the reduced number of CD8+ cells,rather than CD4+ T cells,B cells or NK cells.

Innate immunity against SARSCOV2:

Innate immunity is the first line of host defence after transmission it play important role in inhibiting the spread of pathogen.Pathogen- associated molecular patterns (PAMPs) alert the innate immune cell such as monocytes alveolar macrophages natural killer cells and neutrophils to the presence of invalidating virus. Pathogen- associated molecular patterns (PAMs)are detected by the pattern recognition receptors which include cell surface or endosomal toll like receptors (TLRs), retinoic acid inducible gene I(RIG-I) and nod like receptors . PAMP-PRR interactions result in the activation of "inflammation promoting" transcription factors (TF), including nuclear factor Kappa B(NF-κB) and IFN regulatory factor regulatory factor 3(IRF3)leads to the activation of downstream inflammatory signaling pathway and chemokines such as CXCL-10andCCL-2.IFN-I stimulates CD8+ T proliferation promotes B cell activation, antibody production, and class switching (IgM to Ig G) and activates NK cells and macrophages to clear the viruses. Patients who developed severe covid-19 exhibited a marked increase in neutrophils and reduced lymphocytes count compared with patients with mild signs of the disease. Some studies demonstrated that both macrophages and dendritic cell play the important role for viral destruction and immune response induction in mucosal associated lymphoid tissue.

COVID-19 patients have shown excessive activation of circulating HLA-DR monocytes, which has been associated with the onset of respiratory failure, similarly in the presence of IFN-α and GM-CSF, circulating monocytes should quickly differentiate into monocyte derived dendritic cells which are important antigen presenting cells capable of phgocyting viruses and initiatning the adaptive immune response process as well as activating CD4+T cells generating immune memory in the process and refining the body's defence against infection.TNF-α and IL-1β are known as main activators of IL-6 production which is pleiotropic cytokines that induces B cell proliferation assists Cytotoxic T lymphocytes (CTL) activation and involved in triggering hepatocytes to synthesise acute phase reactant proteins such as a serum amyloid A and C reactive protein (CRP). The complement plays as a "double edged sword" in internet immunity against pathogens while anaphylatoxins,such as C3a and C5a Gyan activity means cells and thereby induced the release of various pro-inflammatory cytokines . Toll- like receptors 3 and 7, cytosolic RNA sensor and RIG 1/MDA5 contribute to the identification of the coronavirus. One of the mechanism of antiviral immunity by type I IFN is the activation of IFN-I induced transmembrane family proteins, which inhibit the entrance of the virus and replication in the host cell. IFN-1 tension to have an important role in immune response against SARS-COV and this is one of the most important immunotherapeutic potential in treatment of COVID-19.

Adaptive immunity against SARS -COV-2:

a) **Humoral response**:Recent studies on antibody responses in covid-19 patients have shown that the majority of patients developed by a specific IgM and IgG antibodies after SARS-COV-2 infection. A study by Zhao et.al on 173 COVID-19 patients reported 82% IgM and IgG 64%,while Long et.al studied showed 100% patients were positive for virus specific IgG .Guo et.. Al studied found that 22% IgM of COVID-19 patience confirm by RTq- PCR after 7 days lack of IGM can be justified by the delay in generating a humoral response against SARSCOV-2 how were longer period remind negative for IGM even 22 days after the onset of symptoms .Asymptomatic individuals have a little or no capacity to produce neutralizing antibody (nAb) while in SARS-COV-2 patients Th 2 cells presents The viral antigen to the B

lymphocytes which subsequently produce neutralizing antibodies against the spike yes protein of the virus is positively correlated which is one of the main concepts for vaccine design against SARS -COV-2 . Decreasing levels of memory B cells will also be found against SARSCOV-2 In recovered patient B cell receptor increases.

b) Cellular response

Virus specific CD8+ cytotoxic cells represent the effector part of cell mediated immunity against viruses. However their activity as well as the activity of these cells is closely regulated by CD4+ T helper cells which are further divided into Th1,Th2,Th9,Th17 and Treg functional Phenotypes. Covid-19 patients it has shown that CD4 and CD8 cells,B cells and NK cells reduced. Exertion and letter depletion of T and NK cells impede antiviral immunity and contribute to the infection registers and lethal stage.NKG2A, expressed on NK cells and CD8+ cells is an inhibitory receptor amplified by Il-6 and IL-10 this hatred aymeric in heavier receptor prevents NK cells from releasing IFN-γ. Previous studies reported that neutralizing antibody for s protein are rasing during the second or third week in SARSCOV, in case of SARS-COV-2 antibody response may emerge earlier . Human leukocytes antigens are critical genetic compounds in APCs that affect the expression of the pathogen antigens to the T cells through MHC -1 , responsible for the cellular immune response against SARS-COV-2. Dysfunction of cellular immune response in COVID-19 is the exertion of the T cells. T cell separated from COVID-19 patients have an increased expression of programmed death-1(PD-1) and T- cell immunoglobulin and mucin- domain containing (Tim-3) surface marker of the T cell exhaustion.

Immunotherapies

Cytokine Storm and cytokines based immunotherapy

Salman M.Toor,Reem et.al studied showed" Cytokines Storm" refers to plethora of proinflammatory cytokines and chemokines observed as pathological features in covid-19 patients various immune cells types including macrophages B and T cells, neutrophils and natural killer cells can contribute to cytokines storm and inflammatory response in covid-19patients .IL-1β is the main characteristics of cytokine storm story of Valle et al showed that IL-6 and TNF – α (tumour necrosis factor) are negatively correlated with total T cell count in mostcaseofcovid-19.The level of cytokines is higher in severe as compared to no severe covid-19 such as tumor necrosis factor (TNFα) IL-2,IL-7 and chemokines such as granulocyte colony stimulating factor (GCSF) interferon Gamma induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP1).In theory a type I IFN -mediated response activates the JAK- STAT signalling pathway that should suppress viral replication and prevent virus from spreading . IL -6 blockers such as Sarilumab,Situximab and Tocilizumab and IL- 1β receptor blocker can have therapeutic efficacy in treatingcovid-19 .while monitoring the production of type 1 IFN in covid-19 patient a peak of IFN-I α2 studied found by Shamsah H. Al-Ahmed et.al . between 8-10 days after onset of symptoms zhou et al conducted a study that demonstrated SARS-COV-2 infection included a markedly elevated expression of IFN -related inflammatory genes which appears to decrease over time in build cases but not in severe ones hyper inflammatory condition related to multiple organ failure and cytokines Storm previous sepsis studies established that IL-6 concentration might be an indicator of the magnitude. Modulation patients with COVID of Systematic immune responses may19 .Anticytokine therapy such as IL of hyper have a potential role in the treatment of 6,TNFα and IL been suggested for alleviation.respiratorydistress syndrome (ARDS) in patients with inflammation as the main leading COVID-19 antagonists have cause of severe adult 19.YinhuaZhang et.al studied showed that 19 patients recovered by treatment of Tocilizumab out of 20 with Severe disease in COVID results.

Therapeutics against Cytokine Storm

Title and register number	**Drugs**	**TherapticTargets**
A multicenter,singlearm,open label trial for the efficacy and safety of CMAB806 in the treatment of Cytokine release syndrome of COVID-19 (ChiCTR2000030196)	Tocilizumab	Anti-IL6Receptor
A Study to Evaluate the Safety and Efficacy of Tocilizumab in patients with Severe COVID19 Pneumonia. (NCT04320615)	Tocilizumab	Anti-IL6Recepto r
Tocilizumab to Prevent Clinical Decompensation in Hospitalized,Non-critically ill patients (NCTO4331795)	Tocilizumab	Anti-IL-6 receptor
Anti -IL 6 Treatment of serious COVID-19 Disease with Threatening Respiratory Failure (NCT04322773)	Tocilizumab+ Sarilumab	Anti-IL-6 receptor
Efficacy of Intravenous Anakinara and Ruxolitinib during COVID-19 inflammation (JAKINCOV) (NCT04366232)	Anakinara + Ruxolitinib	Anti-IL-1 receptor +JAK inhibitor
Efficacy and Safety of IFNα2β in the Treatment of Novel Coronavirus Patients.(NCT04293887)	IFN-α2β	Boost Innate Résistanc e
Administered subcutaneously for COVID-19	Lopinavir/ritonavir+ ribavirin and IFNβ/b	Pulmonary vasodilator

treatment (NCT04276688)		
Low dose of IL-2 in Acute Respiratory Distress syndrome related to COVID-19 (NCT04355364)	IL-2	Anti inflammatory
Ruxolitinib for Treatment of COVID-19 induced Lung injury ARDS (NCT04359290)	Ruxolitinib	JAK inhibitor
Unit of IFN α-2b accompanied by vapour inhalation twice a day guideline for COVID-19 treatment	Ribavirin	Antiviral drug pulmonar y Vasodilat or

Convalescent Plasma therapy(CPT):

Neutralizing antibodies collected from hyper immune patients through plasma transfusion is one of the most accessible approach against viral infection this method called Convalescent plasma therapy (CPT) shows the promising results in SARS and MERS patients.HajarOwji et.al and Rabban Ali A.et.al studies showed this approach first time used during outbreak of Spanish influenza the effectiveness of CPT varied according to the type of microorganism its pathogenesis and treatment protocols.HajarOwji et.al reported that treatment is get failed in 76 year old covid-19 lymphoma patient when treated with bendamustine and rituximab later on second treatment is given, administration of hyper human plasma resulted in a rapid recovery in patient . Leila Mohamed et.al andArmen Yuri Gasparyan et.al studied shwoed CP therapy efficacy on critically ill covid-19 patient in China.5 patients of COVID-19 treated with CPT out of them 4 patients showed improved condition within 12 days . Leila Mohamed reported one study that CP therapy was initiated 10-12 days after administration .In Duan et.al reported median time for plasma transfusion was 16.5 after disease onset . A minipool of pathogen reduced CCP with an elevated dose of neutralizing antibodies from at least two CCP donations or a second viable preparation alternative namely a homologous standardized cryosupernatant with fixed potency of neutralizing antibody .MasoomehMasoomikarimi et.al Studied found that Convalescent plasma has two important effects via it's composition in the in the improvement of COVID-19 patients.An antiviral effects via neutralizing antibody and an immunomodulatory effect Via anti – inflammatory Cytokines & antibodies . While TugceNur et.al study reported that WHO suggested the use of CP as vaccines and antiviral drugs are not available in COVID-19 treatment . Nicolas Vabretet.al reported that CP therapy show improved Outcomes but RCTs are needed to confirm this,several clinical trials are currently in progressworldwide. A study of ManeulRojas,Yhojan Rodriguez et.al reported that on 24 March, American Food and Drug administration recommended " COVID-19 Convalescent Plasma Research Emergency declaration, the plasma obtained from donors and transfused in the recipients on same day lead to viral load decreased the tire of IgG and IgM in recipient increased in a time- dependent manner . Modern Screening of donor plasma for blood- borne pathogens and blood type, decreases the risks of transmission of infectious diseases including the potential pathogen being treated and reactions to serum including serum sickness .

Immunomodulators:

Immunomodulatorsare substances that affect immune system function, representing a potential therapeutic strategy for COVID-19. Li Yang,Shasha et.al Studied reported that IFN α2a and 2b abroad for treatment of hepatitis B and C virus used to stimulate innate antiviral responses in patient. Amino modulators pseudomonas aeruginosa and thymosin may be effective for COVID-19 treatment due to their immune regulatory functions .

JAK inhibitors: Janus associated kinase (JAK) and members of num- associated kinase (NAK) family including AP -2 associated protein kinase 1 (AAKT) are two main regulators of endocytosis, as SARS Cov 2 may also enter the cell through clathrin mediated endocytosis, JAK Inhibitos include ruxolitinib , baricitinibfederatinib which are mainly used for treatment of myelofibrosis. JAK inhibitors are considered as relativly safe therapeutics for SARS Cov -2 that inhibits INF α.

UTI: Ulinastation an active trypsin inhibitor in urine actually it is nature Serine protease. Trypsin inhibitor can also stabilize cell membrane, inhibit calcium influx and NF - K, B acltivation and antagonize oxygen free radicals. UTI has been recommended for anti therapy in china. In COVID-19 S protein 19 b protein binds to ACE2 also to be activated and cleaved by transmembrane protease Serine (TMPRSS2) camostat and nafamostat can prevent S protein from activation and cleavage through inhibiting TMPRSS2 and prevent membrane fusion.

Intravenous Immunoglobulin: Intravenous Immunoglobulin is a pooled preparation of normal IgG obtained from healthy donors generally used in immunotherapy of most of the autoimmune and inflammatory disease by blocking Fc gamma receptors and neutralizing inflammatory cytokines.On the on set of COVID-19 infection initial administration of high dose IVIG reports the promising results . Studies of Masoomeh et.al and AnthonyG.Tsolaki et.al showed that 48 Hr. ICU patient with SARS-COV2 patient reduce the use of mechanical ventilation and 28 day mortality rate due to treatment of IVIG.another study reported that 300 patients administrated with high dose of IVIG made a satisfactory recovery. Another study reported that corticosteroids combined with IVIG (20gm/day) with short term and moderate dose is administrated to COVID-19 patients might be beneficial.study on methylprednisolone combine with IVIG treatment shows positive results in Wuhan China demonstrated elevation of lymphocytes counts decreased of inflammatory markers partial or complete results in specific lung affection and negative nasal and oropharyngeal swab test within a few days of therapy. Critically ill patient should be treated with IVIG therapy combined with IL6 and IL1 targeted immunotherapies.

Immunecheckpoint inhibitors: Salman M.Toor,ReemSaleh et.al reported SARS-COV2 infection may induce T-cell exhaustion by increasing the expression of inhibitory immune checkpoints. Marisa Market ,Leonard Angka et.al studied found checkpoint inhibitory receptor including CTLA4 and PD1 as a key regulators CTLA4 and PD-1/PDL-1 blockade shows the positive results in cancer immunotherapy that lead a step for the use of these drugs in COVID-19 patients,PD1 has also been shown to play a role in regulating NK cell responses, in addition to modulating T-cell function and increased in COVID-19 patients .

Mesenchymal stem cell therapy (MSCs): MSCs possess limitless self renewal and multipotency with antiinflammatory effects that defend against

cytokine storm repair pulmonary epithelial cell damage and promote alveolar fluid clearance . 65year old women with COVID-19 treated three times human umbilical cord MSCs (hUCMSCs) with a three day interval with injections of thymosin α1 antibiotics computerized tomography (CT) and showed an improvement in inflammation and symptoms after 4 day RTPCR and Swab test report was negative intravenous transplantation of ACE-2MSC in seven patients showed safe and effective treatment of SARS-COV 2 infected patients . Mesenchymal stem cell have several advantages such as intrinsic clinical properties, adequate clinical-based studies and the ability to store as cell banks that due to banking ability allogeneic sources Of MSCs are used in clinical application frequently .

Natural killer cell:

Natural killer cells are key component of innate immune system that comprise 10-15 percent of total peripheral blood leukocytes.First immune components contributing to initial response against virus infected and cancer cells .Natural killer cell therapy has been approved in china to contribute to antiviral defence and enhance the immune response in COVID-19 patients, antibody recruiting molecule (ARMTM) is a synthetic molecule and has three binding regions such as spike protein, linker and antibody ARM can bind both to the virus and immune cell via FCYR in clearance of virus by NK Cells .

DC Therapy :

The application of engineered DCs is mainly a hot topic in Cancer therapy . A-C type lectin expressed on surface of DC called Dendritic Cell Specific Intercellular adhesion molecule Grabbing No integrin (DC- SIGN) was found to play important role in attachment of many viruses to host cells such as HIV DC -SIGNR also called L -SIGN is a homology of DC-SIGN and promotes many infection with SARS Cov-S particle. Mona Kamal Saadeldin et.al reported in their studied that antibodies against DC-SIGN inhibit some of DC infection and could serve as a promising target for designing novel ttherapies.

Lymphopenia:

It was shown that about 85% of the severely the patients of COVID-19 are suffering lymphopenia . lymphopenia means low counts of lymphocytes in blood, NazaniFathi et.al and Mohsen Rokni et. al reported CD8+ and CD 4+ cells reduced particularly in elderly patients more than 60 years.Rokniet. al studied found, SARS-COV-2 induced in in lymphopenia is not clear but in general lymphopenia can occur by three different mechanism _ a) decrease the production of lymphocyte b) apoptosis and destruction of lymphocytes c)Lmphocyte redistribution through attachment and migration of lymphocytes through endothelial cells, lymphopenia and enhanced and NLR are highly correlated with COVID 19 disease . A recent study of MasoomehMasoomikarimi et.al showed that ICU COVID19, SARS-COV show . lymphocyte count of 800 &hypercytokinemia.Decreased lymphocytes count in severe case of COVID-19 could be influenced by two factors first direct cytotoxicity of virus on immune cells such as T lymphocytes and second host factors including diabetes ,hypertension and cardiovascular. Another hypothesis IL 6 may inhibit T cell mediated immunity which is associated with lung lesion in acute phase COVID19—patients.

Monoclonal antibodies:

The development of antibodies protecting during SARS -COV-2 infection is an urgent public health and vaccine development to show the majority of SARS-COV-2 patients produce antibodies specific for S protein and RBD. Carlos Cruz- Teran reported the regeneron is also conducting Phase 1/2/3 trials testing the safety and efficacy of antibody Cocktail REGN-COV2 in infected patients,(NCT04452318) .A study of Samuel k Lai.et.al reported the emergency use authorizations of REGN-COV2 and LY-COV555 both exclude usage in Hospitalized patients due to poor results from clinical trials (19) B- lymphocytes are collected from patients who have recovered from covid-19 and it is seen that cells are capable for producing the required neutralizing antibodies and cloning blocking monoclonal antibodies (mAbs) is a labour intensive task. Clone mAbs reported high Titres of IgG Antibodies against D1 subunit and receptor binding locus in the majority of recovered patients Invitro human monoclonal antibody 47D11 prevents the replication of SARSCOV-1 and SARS-COV-2. Another study suggest that 48 healthy individuals potential precursor sequence have been identified in native B cell. SARS-COV-2 diverse set of precursors can help to produce neutralizing antibodies study reported that monoclonal antibody CR3014 neutralizes SARS -COV-2. CleaMelenotte et.al and Ali A. Rabaan et.al reported compared hospitalized patients with outdoor patients or convalescent plasma donors and identified that in a hospitalized patients 3000 fold higher antibody is one of the limitations .Takeda Pharmaceutical company based in Japan is in the process of preparing a monoclonal antibody mixture TAK-888 from serum of recovered COVID -19 patients .Some studies reported Conservation of the particular residue that are essential for formation of specific bond between RBD and antibody, between two viruses cross neutralization capacity of antibodies the residue was for the formation of salt bridge and electrostatic interaction between M396 ab,RBD were conserved between SARS-COV-1 and SARS-COV-2 CR3022 also bind to the receptor binding protein (RBD) which is located in D1 subunit of S proteins of SARS-COV-2 and inhibit it whereas CR3014 and M396 neutralizes SARS-COV-1 but failed to bind SARS -COV-2protein..Development of resistance to antibody cocktails might originate from relatively high mutation rates of SARS-COV-2,COVI – shields from Sorrento contains mixture of three antibody against three regions of SARS-COV-2.Spike.Protein. GSK &Vir candidates VIR 7831, VIR- 7832 and antibody from regeneron Eli Lilly and Celltrion. REGN_COV-2 antibody Cocktail is currently undergoing clinical trials as a part of recovery collaborative group trials (NCT04381936).MasoomehMasoomikarimi,et.al and Jeffery S.et.al studied reported two classes of IL-6 inhibitor; monoclonal antibodies Sarilumab,Tocilizumab against IL-6 receptor approved by FDA.

Conclusion:

The global fight against Coronavirus Disease 2019 requires concerted efforts, Still there is no proven specific vaccine or drug treatment against COVID-19 due to unknown structure of SARS-COV-2. There is a major point to study that, How human immune system give responses as virus enter into human body therefore the improved understanding of virus structure and it's destructive actions with hyperinflammation and dreatful systemic manifestations points to the necessity of a multidisciplinary approach. Monoclonal antibodies shows promising result but there is limitation, Use of Convalescent plasma and MAbs might be significant for patients not be useful for Population.Immunomodulators also show promising results in

COVID-19.In this review many immunotherapies are discussed but one of the potential approach therapy is use of IL-6R blocker to control hyperimflammatory responses could be used in COVID-19 patients as well as use of JAK inhibitors to manage Cytokine storm which reduces lung tissue damage in COVID-19 patients. IN addition, strategies to suppress viral replication and prevent virus from spreading IFN-I therapy could have be promising results in treating COVID-19.The future aspect is, Lymphopenia is seen in diabetes, hypertension, cardiovascular that seen in COVID-19 elderly patients as most of the deaths caused by COVID-19 in those patients who has low immune system so by getting appropriate therapy on Lymphopenia,we will get a significant results against COVID-19. Currently, precaution is one of the most important factor to avoid infection.

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