OPEN ACCESS

Saudi Journal of Medicine

Abbreviated Key Title: Saudi J Med
ISSN 2518-3389 (Print) |ISSN 2518-3397 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Review Article

Approaches to Immunotherapy, Drugs for Treatment of COVID-19, Mechanism of Action and Challenges

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DOI: 10.36348/sjm.2021.v06i05.007 | **Received:** 06.04.2021 | **Accepted:** 09.05.2021 | **Published:** 27.05.2021

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Abstract

Coronavirus has taken it serious form and also causes the death once damage the air passage ways into particular host. This virus is transmitted from the air droplets of the infected person. There are variety of responses agonist the Covid-19 by innate immunity that particularly recognized the cells of this virus as a pathogenic form and fights against them. It can be recognized through the pathogen associated molecular patterns. Type I IFNs are mainly involved in activation of other cells of immune system that contribute to immunity. Helper T cells are the main cells for defense against the viral cells. Helper T cells are the directors of the cellular immunity against SARS-CoV-2. There are different parts of the adaptive immune system work together, so seeing Covid-fighting antibodies, memory B cells, memory CD4+ T cells and memory CD8+ T cells in the blood more than eight months following infection is a good sign. Remdesivir as one of the antiviral drug binds to the particular cells of virus at cellular level by binding to the viral RNA. Tocilizumab as one of the approved drug by FDA for treating the Covid-19. Dexamethasone is used as potential drug to reduce the severe inflammation against the caused by corona virus. This drug has shown positive effects against the Covid-19.

Keywords: Covid-19, immunotherapy, drugs, Dexamethasone, inflammatory responses.

INTRODUCTION

Covid-19 as one of the most infectious virus that affected the people all around the world. This virus also blocked the transport and also influence on the economy of world [1,2]. This virus has taken it serious form and also causes the deaths once damage the air passage ways. This virus is transmitted form the air droplets of the infected person. Once it enters into lungs, stat damaging the lungs as well as respiratory tract. This virus takes its form from one to fourteen days in order to replicate in the particular host cell. After that, visible symptoms appear in the different parts of body especially body organs such as lungs [3, 4, 5].

Different symptoms appear once Covid-19 enter into cells of particular host and start replicating [6, 7]. The most common symptoms appear as the cold, cough and shortened breath due to which enter into repository tract. It ultimately blocks the air passage airways. Some studies reported that fever and shivering also appears during replication of this virus. These symptoms appears in the different organism of the body and patient needed critical care in poorer to beat the virus from body due to maintain the healthy style and boost the immune system [8, 9].

Innate Immunity against SARS-COV-2

There are variety of responses agonist the Covid-19 by innate immunity that particularly recognized the cells of this virus as a pathogenic form and fights against them. It can be recognized through the pathogen associated molecular patterns. There are different types of receptors that helpful for the identification of the corona virus. These are Toll- like receptors 3 and 7, cytosolic RNA sensor [10]. After recognition in particularly response by innate system, there are different types of proteins that activate the

signaling pathways as the phosphorylation of nuclear factor κB (NF-κB), phosphoinositide 3 kinase, and IFN regulatory factor 3 (IRF 3). This type of activation leads to the activate of the cells of inmate system that relapses or produce the special type of proteins in response to this virus such as type 1 interferon's(type I IFNs) [11,12].

Type I IFNs are mainly involved in activation of other cells of immune system that contribute to immunity [13]. These are natural killer cells that take the most active response against the Covid-19. Natural killer cells have dual functions as recognize of coronavirus cells as well as killing them in particular way. Natural killer cells are involved i exert of major histocompatibility complex that are involved to recognized the cells of the Covid-19 in resume to their attack on the particularly cells of immune system. Respiratory cells affected due to attack of Covid-19 virus due to which immune system releases the dendritic cells. These cells involved to fight against the viral infection as a part of immune system. They bind to the viral protein and inhibit their replication in order to replicate of extending virus. Dendritic cells also activate the antigen presetting cells that also recognize the special proteins on the surface of the virus. Different studies have been made to investigate the structure of Covid-19 proteins and its configuration [14,15].

Different types of proteins as well as proteins and transcription factors invoked in the immune responses in response to attack of Covid-19[16, 17]. Each cells of immune system or particular proteins its own function in recognizing and killing the cells of immune system. Covid-19 has rapid mode of replication and hence more chances of attack to host when entry into the body. This virus has main target the cells of air passage ways and cells of lungs which air flow in this block. It resulted the suffocation and needed oxygen in order to survive. This virus appears more chance of attacking to normal cells once transmitted from the infected person [17,18].

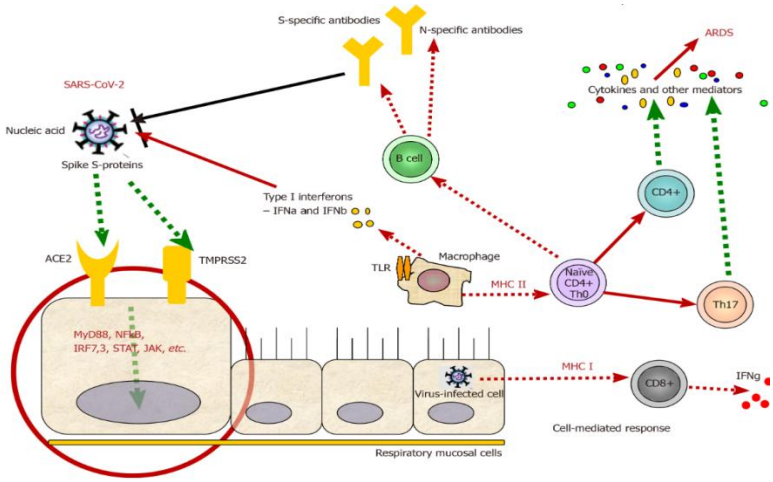

Fig-1: Shows the inflammatory immune responses against the SARS-COV-2

Adaptive Immunity against SARS-COV-2

Helper T cells are the main cells for defense against the viral cells. Helper T cells are the directors of the cellular immunity against SARS-CoV-2. In COVID 19 patients, the serum levels of the Th1 associated cytokines are reported to be increased [19, 20]. CTLs attack the viral contaminated cells and destroy them by the producing performing and granzyme. These activate the immune system by destroying the viral proteins as well. Also, Th2 cells present the viral antigen to the B lymphocytes, which subsequently produce neutralizing antibodies against the spike (S) protein of the virus. The neutralizing antibodies inhibit the replication of the virus inside the body and produce humoral immunity, which is one of the main concepts for vaccine design against SARS-CoV-2. Vaccine for Covid-19 needed clinical trials to pass for its use to human body as this vaccine worked against the viral cells [21, 22].

T helper cells also involved to activate and releases the different types of interferon's. Th17 cells are another subgroup of the helper T cells that have been reported to be increased in COVID- 19. The production of IL-17, a proinflammatory cytokine, by Th17 cells, promotes the inflammatory response. The exact mechanism of the antiviral function of the Th17 cells, another group of cellular immunity, has not been determined yet. Th17 cells could have antiviral function through the production of inflammatory cytokines; however, further study is required to understand the exact antiviral role of Th17 cells as this virus replicate more readily due to its stable structure and complex proteins in making its torture [23, 24].

The different parts of the adaptive immune system work together, so seeing COVID-fighting antibodies, memory B cells, memory CD4+ T cells and memory CD8+ T cells in the blood more than eight months following infection is a good sign. As well as T cells, humoral immunity, mostly through B cells, has a significant role in the induction of adaptive immunity

against coronaviruses. The activation of the B cells and the plasma cells leads to the production of the neutralizing antibodies that prevent further contamination by the virus. Immune B cells, which help to hunt down invaders circulating in the bloodstream by producing antibodies - proteins which can bind to e.g. viral particles and either neutralize or mark them for destruction by other immune cells [25, 27].

T cells, which seek out and destroy cells that have been infected by the invading pathogen by recognizing tell-tale proteins on their surface [27, 28]. T cells also support B cells, helping to control the antibody response. Appropriate antiviral antibodies prevent the patient from being reinfected by the virus; however, it has been recently reported that inadequate serum antibody levels could expose the patients to reinfection. Besides, some cases of reinfection have been reported, which questions the humoral memory immunity against SARS-COV-2. Further research is needed to be inducted for understanding the accurate immune response mechanism to the SARS-COV-2. SARS-CoV-2 specific T cells and B cells have major roles in the immune response in COVID 19 and thus, must be considered as promising approaches in rational drug and vaccine design against COVID 19[29, 30].

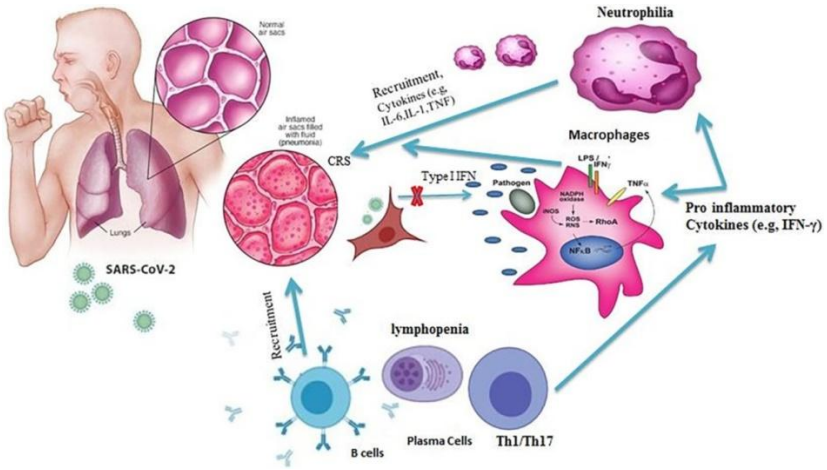

Fig-2: Shows the alternative mechanism of SARS-COV-2 and various responses by immune cells

Mechanism of action of Remdesivir

It binds to the particular cells of virus at cellular level by binding to the viral RNA. It cannot proliferate the chain of initiation of the viral proteins. It binds at the replication origin and thus inhibiting the overall replication in order to further attack of respiratory tract and other problems in lungs [31, 32, 33]. This drug particularly works only for the human as a antiviral to activate the immune system of infected person to fight the cells of coronavirus. This drug could be used only in normal concentrations. Higher the concentrations of the dose, higher the activity to work against viral cells only at optimum level of drug achieved. Lower the concentrations of the dose lower the activity to work against viral cells only to stimulate the cells of immune system to fight against the viral replication [34, 35].

Rationale for use in the Treatment of COVID-19

Different literature shows the activity of remdesivir in vitro and in vivo in experimental animals to show the clinical investigation for its use in the human as a potential drug [36, 37]. It has shown severe side effects if use in over dose concentrations that damage the cells of lungs by causing the autoimmunity. In order to given this drug, it should be noted the concentrations of coronavirus that replicate in the particular cells. Wring use of this drug leads to toxicity to their major organs such as liver and lungs. This drug is under the clinical experimentation for their treatment of Ebola virus that is the most deadly virus and affected the large populations all around the world. In comparison to coronavirus, Ebola has less affected the populations all world the world [38, 39].

Mechanism of Action of Tocilizumab

Tocilizumab as one of the approved drug by FDA for treating the Covid-19. Since, it has been used as corticosteroid to treated the arthritis. It has effective drug for treatment of Covid-19 due to its potential effects [40, 41]. This drug has shown active role in blocking of viral signal transduction. It particularly binds to the viral antigen that involved for replication due to which its signals to block the activity of viral RNA. This drug has shown the maximum activity as compared to the other drugs in blocking of signal transduction. This drug has reduced the symptoms of patients of Covid-19 due to its strong action also fever control during viral replication. This drug has now side effects on the body while complications occurred due to its overdose. This drug clinically approved for reducing the inflammation as well as fever conditions [42, 43].

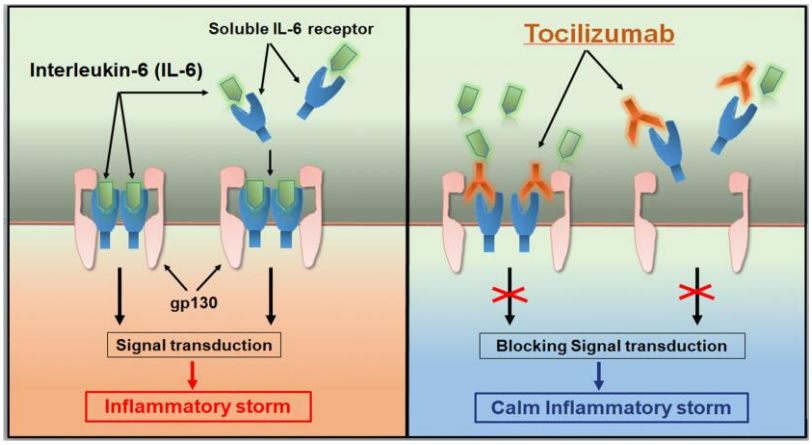

Fig-3: Shows the mechanism of binding and action of Tocilizumab

Mechanism of Action Dexamethasone

Dexamethasone is used as potential drug to reduce the severe inflammation against the caused by corona virus [44, 45]. This drug has shown positive effects against the Covid-19. It is sued in the different formulations either in the form of tablets, capsules as well as injections. It typically binds to the viral RNA and inhibits their replication. It has shown show biding to the viral cells with reduced information in ways either strong binding and weak binding. Strong binding to the Viral RNA leads to strong activity of this drug and hence block the replication. Low activity of tis drug leads viral RNA leads to low activity of this drug and hence increase the chance of the viral replication and hence more chances of inflammation [46].

CONCLUSION

Different types of drugs are recently effective for the treatment of Covid-19 but many previous studies of SARS CoV, Middle East respiratory syndrome related coronavirus (MERS CoV), and other coronavirus vaccines revealed several safety concerns associated with the use of coronavirus S based vaccines, including inflammatory and immunopathological effects such as pulmonary eosinophilic infiltration and antibody- dependent disease enhancement (ADE) following subsequent viral challenge of vaccinated animals. There is need to design such drug with no side effects on the body organs.

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