Monoclonal Antibody Therapy In Covid-19

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Abstract

The treatment for viral diseases has always been critical and has been a serious matter of concern. The treatment for the viral infections may be through drugs but mostly relied on vaccines and formation of antibodies. In the present day research, monoclonal antibodies are the major area of treatment for viral infections. The previous infections similar to COVID-19, SARS and MERS, have been studied for the monoclonal antibody treatment. The present review concentrate on the monoclonal antibody therapy that may be effective against the COVID-19 infection.

Keywords- COVID-19, monoclonal antibodies (mAB), Monoclonal antibody therapy.

INTRODUCTION

The history of virus and disease producing effect of virus developed long back in the science. Most of the viral diseases caused are usually not treated with any type of medication. The reason that lies behind the concept is that they cause self limited illness which does not require any antiviral therapy. But in the last few years certain virus like Hepatitis C virus (HCV), Ebola virus, Marburg virus, Severe Acute Respiratory Syndrome (SARS) virus, H5N1 bird flu virus, H1N1 influenza virus, trH3N2 virus, trH1N2 virus, Hendra virus, Nipah virus, yellow fever virus, and West Nile virus had created much damage to the human population with fatalities. The present situation of the pandemic created by COVID-19 has panicked the entire world. Out of the various diseases caused the present antiviral drugs usually target mainly three viruses herpes, hepatitis, and influenza [1]. The viral diseases at a wide range are treated with vaccines. It is since 1920 the development of vaccine started against diphtheria and WHO launched its plan from 2011-2020 as the "Decades of Vaccines—Global Action Plan 2011–2020" [2]. The vaccines act on the immune system of the body to fight against the pathogens or antigens [3]. The more recent research on the treatment against the viral infections includes the use of monoclonal antibodies (mAB). The palivizumab was the first mAB used as prophylaxis against Respiratory Syncytial Virus (RSV) infections [4]. In the present pandemic situation a multiple research is going on for prevention and treatment of COVID-19 with different category of substances. The various antiviral drugs, different antibiotics are being used to overcome the symptoms of COVID-19. The present world has entered into the discovery of various drugs for the treatment against COVID-19. In this discovery, vaccines and mAB has taken the lead role to effectively enhance the immune mechanism of the body as immunological actions are most effective against infectious diseases [5].

This paper is related with the monoclonal antibodies along with its mechanism of action and the effect of monoclonal antibodies in the treatment of COVID-19.

Mechanism of action of monoclonal antibodies:

The basic mechanism that is used for treatment of viral infection with the monoclonal antibodies is the process of passive immunization [6]. The antibodies that are being used for the treatment of various viral and infectious diseases works by the following mechanisms:

a) **Neutralization-** The antibodies neutralizes the virions by recognizing the surface antigen of the virus which is required for binding to the host cell [6]. These antibodies block the pathophysiological functions of virus [7].
b) **Antibody dependent cell mediated cytotoxic reactions (ADCC)-** This is the process of cell mediated immunity. In this process the Fv binding domain of the antibody binds to specific antigen present on the surface of the virus (target cell). The antibody activates the immunological cells like macrophage of NK cells and bind to the Fc portion of the immunological cells. Various cytotoxic granules are released which kills the virus the target cell [8].
c) **Complement dependent cytotoxic reactions (CDC)-** In this mechanism the antibody binds to the complement component C1q and activates the classical complement cascade where the cytolytic end product of the cascade lyses the viral cell targeted [8].
d) **Antibody dependent cellular phagocytosis (ADCP)-** Here the viral cells that are bounded by the antibody are phagocytosed by the immune response cells like macrophage, granulocytes and dendritic cells. The Fc portion of the monoclonal antibodies interacts with the Fc portion of the phagocytic cells [9].
e) **Antibody dependent cell-mediated virus inhibition (ADCVI)** – in this mechanism the viral spread is decreased. Here the cell infected with virus is targeted. These infected cells express various FcgRs (a type of Fc receptor) through viral specific antibodies. This ADCVI measures the effect of antibody and FcgR cells on virus. The ADCC and chemokines destroy the virus and its spread [10].

Monoclonal antibody portions:

Fab fragment: This is the antigen binding region of the antibody having one constant domain and one variable domain with both heavy and light chains.

Fc fragment: It is the crystallizable region of the antibody that interacts with Fc receptors (present on cell surface) and helps in activating the immune system of the host.

Fc receptors (FcRs): To this receptor the Fc fragment of immunoglobulins binds [6].

Monoclonal Antibody Therapy

The virion and the infected cell in certain condition form the immune complexes with the monoclonal antibodies. These complexes are recognized by the antigen presenting cells (APCs) that are responsible for adaptive immune responses. As APCs are the central unit so they are responsible for endogenous immunity by activating cytotoxic T-cell responses.

The use of monoclonal antibody is the immunotherapy which activates the body immune system against infectious diseases [5]. In various viral infections like influenza, SARS, MERS, and Ebola use of stimulant plasma or immunoglobulin was affective against mortality rate [11,12,13]. The monoclonal antibodies have high specificity for a particular molecule in the body which can alter the mechanism of the virus activity or infected cell and therefore becomes a specific treatment for a particular disease [14]. The monoclonal antibodies can easily identify an epitope on the virus and prevent its proliferation [11].

Pathological conditions on Monoclonal antibody therapy

Many of the monoclonal antibodies block the physiological pathway of the antigens as a result of which many of them has found to interfere with the physiology of the normal cell of the host body. There are certain examples of such drawbacks of monoclonal antibody therapy. Bevacizumab has been found to reduce angiogenesis in healthy cells as it blocks the signal transduction of vascular endothelial growth factor (VEGF) [Lyseng-Williamson and

Robinson]. Cetuximab blocks the signal transduction of epidermal growth factor receptor (EGFR). Its use has found to bring about the dermatological lesions and epidermal changes [15, 16]. Similarly, Rituximab has been found to inhibit the expression of CD20 B cells [17].

All the effects observed were in the nonclinical studies. And all these drugs are indicated in the anticancer therapy rather than antiviral therapy. As the antibodies have high specificity so they target the receptor wherever they are present in the body. Moreover the cytotoxic antibodies usually show such type of toxicity in the body at many times. But as the immune regulatory factors are involved in such type of reactions so even there are instances that even if the same target is expressed in the host cell but the monoclonal antibody do not show any cytotoxic effect [7].

Structure of COVID-19

In the last few decades corona virus has been cause of viral diseases in humans. Two of them have been under research over the last two decades: Severe Acute Respiratory Syndrome CoronaVirus (SARS-CoV) and Middle East respiratory syndrome (MERS)-CoV. Most recently, the corona virus which has brought the pandemic situation is Severe Acute Respiratory Syndrome CoronaVirus-2 (SARSCoV-2) or COVID-19.

Corona viruses of all types have the similar morphological and chemical structure. The viruses have an envelope containing single-stranded (positive-sense) RNA. The nucleoprotein is enveloped within a capsid. The viruses are spherical or polymorphic in shape with the presence of spike protein [18]. The virus in the structure mainly consist of four structural proteins: the spike protein (S), membrane protein (M) and envelop protein (E) and nucleic capsid protein(N) [19] as given in figure 1.

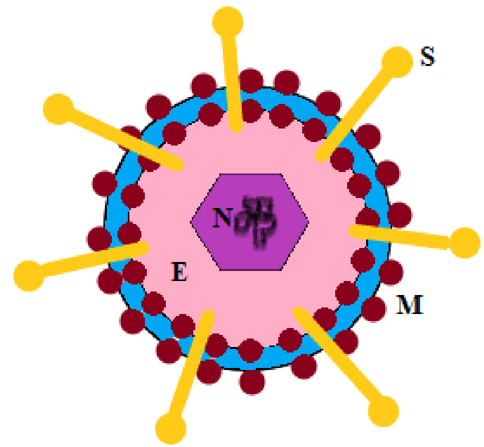

Figure 1: Structure of Corona Virus

The spike proteins of COVID-19 indentify the receptor on the host cell and the interaction begins in the body. There are two subunits in the spike protein of the COVID-19 that helps in the cellular attachment of the virus on the cell membrane of the host. The COVID-19 and SARS virus have high genetic similarity with about 77.5% similar amino acid sequence of the spike protein [20, 21]. The subunits of the spike protein of COVID-19 indentifies the ACE2 (Angiotensin converting enzyme 2) receptors of the human epithelial cells. The viruses bind to this receptor and enter into the host cell and the viral life cycle begins within the host cell [18, 19, 22] as given in figure 2.

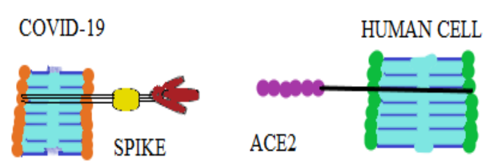

Figure 2: Mechanism of attack of COVID-19 on human cell

Monoclonal antibody therapy in COVID-19

Several studies have suggested the structural similarity between the SARS covid virus and COVID-19 structure therefore, as the monoclonal antibodies were effective against the SARS covid virus so it also be effective against the COVID-19 virus [23, 24]. Due to structural and pathogenesis similarity of COVID-

19 and SARS-CoV several antiviral monoclonal antibodies suggested against SARS was used in COVID-19 patients [25]. The aim in the therapy of monoclonal antibody in most cases is to block the spike protein subunit S1 so that it will inhibit the ACE2 identification and binding to the host cell [12,13]. The monoclonal antibodies some types recognize the epitopes in unit S2 of COVID-19 and helps in neutralization reaction [26].

A research is being conducted on the human neutralizing antibodies that have been found to block the action of COVID-19 virus. The studies on the three new antibodies- B38, H4, 47D11 has been found to effectively neutralize the corona virus infection. Among these three antibodies the 47D11 is effective against both COVID-19 and SARS-CoV but the other two is effective only against COVID-19.

In another study conducted on COVID-19 recovered patients it was found that Neutralizing antibodies developed in the patients and that remained inside the body after the disease condition. It has been concluded that such antibodies may be used for passive immunization after being titrated [25].

Challenges and Future prospect in the therapy with monoclonal antibodies

The large scale production of monoclonal antibodies is required during the time of epidemic or pandemic which becomes time consuming and expensive. The situation is most challenging as during pandemic condition the therapy should be made available to all categories of the population. The condition may be overcome if cloning and expression process is done in other species like yeast, plants or mammals. This will lead to rapid production of antibody at lesser time and at affordable cost [27,28].

The monoclonal antibody therapy is the most promising method in the treatment of antiviral diseases specially when it is a virus like COVID-19 where drug therapy has been almost impossible. The antibodies are the neutralizing in nature and it is the process of passive immunization. The most effectiveness in this therapy is the specificity of the antibody to an antigen and utilizes the host immune system. In near future the monoclonal antibody therapy will be most promising for the viral infections.

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