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REVIEW ARTICLE

Anti-IgE monoclonal antibodies as potential treatment in COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is associated with irreversible effects on vital organs, especially the respiratory and cardiac systems. While the immune system plays a key role in the survival of patients to viral infections, in COVID-19, there is a hyperinflammatory immune response evoked by all the immune cells, such as neutrophils, monocytes, and includes release of various cytokines, resulting in an exaggerated immune response, named cytokine storm. This severe, dysregulated immune response causes multi-organ damage, which eventually leads to high mortality. One of the most important components of hypersensitivity is immunoglobulin E (IgE), which plays a major role in susceptibility to respiratory infections and can lead to the activation of mast cells. There is also a negative association between IgE and IFN-α, which can reduce Toll-like receptor (TLR) nine receptor expression and TLR-7 signaling to disrupt IFN production. Moreover, anti-IgE drugs such as omalizumab reduces the severity and duration of COVID-19. In addition to its anti-IgE effect, omalizumab inhibits inflammatory cells such as neutrophils. Hence, blockade of IgE may have clinical utility as an immunotherapy for COVID-19.

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Introduction

Coronavirus disease 2019 (COVID-19), as a deadly pandemic, has killed more than 1.5 million people so far [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has irreversible effects on most of the organs, especially the cardiorespiratory system, even in people who have recovered [2,3]. Widespread prevalence of the virus has led to major restrictions for people to prevent its progression [4,5]. These restrictions have imposed severe economic and cultural damage to human societies [6,7]. Therefore, this disease has endangered not only physical, but also mental health [8,9]. One of the challenges of this disease is a severe drop in blood oxygen levels, and many efforts have been made to improve it with the help of drugs and ventilators. This hypoxia is profound and disproportionate and causes vascular dysfunction in the later stages of the disease. This requires an additional vascular and rheological approach, which in turn makes the use of anticoagulants in the treatment of COVID-19 a necessity [10]. Additional complexity of this disease is its numerous clinical manifestations, in which 11 different faces of the disease have been observed so far: patients' symptoms can be categorized in a wide range from asymptomatic from mild to severe, with or without pneumonia [11]. Despite many efforts, the vaccine or definitive cures for the disease has been challenged so far. Therefore, only supportive therapies are available for COVID-19 patients and the main role in patients' survival is still on responsibility for their immune system [12–15]. Therefore, most of the studies have examined the role of the host immune system and its management against the influenza virus and COVID-19 [16–19].

Hypersensitivity of the immune system and COVID-19

In COVID-19, the immune system acts like a double edge sword, because on the one hand, effective immunity is required to fight the virus, and on the other hand, severe inflammation leads to multi-organ damage and is one of the major causes of patient mortality [20,21]. COVID-19 seems to have a three-stage progression. The first stage is the initial infection, the second stage is the pulmonary phase and the third stage is the inflammatory phase. The initial stage is

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attributed to the virus (5–7 days), while the next two stages are thought to be due to the inflammatory response (7–15 days from the onset of the disease) [22]. In fact, SARS-CoV-2 infection differs in several epidemiological and pathological features from many other viral infections. One of them is the high level of cytokine release, which in turn causes an uncontrollable reaction known as the 'cytokine storm'. This phenomenon contributes to Acute Respiratory Distress Syndrome (ARDS), leading to pneumonia and respiratory failure. After the virus reaches the lung tissue, innate immunity drives the inflammatory cascade that fight against pathogens; in this case, SARS-CoV-2. However, this inflammatory activation also leads to severe cardiorespiratory system damage [23]. Therefore, fighting hyper-inflammation and regulating immune function play a very important role in controlling the pathogenesis of COVID-19. Hyper-inflammation in response to viral infection seems to be the main cause of its lethality [24,25]. For this reason, the mechanism of sensitization by viral infections of the respiratory tract is an important research area [26]. In this regard, because of their anti-inflammatory effects, corticosteroids have become an adjunctive therapy for acute respiratory syndrome and help to effectively treat the phenomenon of cytokine storm in COVID-19 [27]. One of the reasons for using this group of drugs is the successful experience of their use in the face of coronavirus 1 (respiratory syndrome) coronavirus (SARS-CoV-1) [28]. Also, clinical observational studies have shown improvement in symptoms and oxygenation in patients with severe COVID-19 who have been treated with corticosteroids: the mortality rate in the corticosteroid group was significantly lower than the non-corticosteroid group (4.3% vs. 15.6%) [29].

Hypersensitivity, asthma, IgE, and infection

One of the most important components of immune hypersensitivity, is IgE, which is also involved in allergies, which comprise the hyper-reactivity of the immune system to a variety of factors. People with allergies have immune systems that overreact to seemingly harmless substances in their habitat. IgE activity releases heparin, histamine, and some other cytokines. These substances also cause systemic reactions, especially in the respiratory tract, causing asthma, which is somewhat similar to the respiratory distress observed in COVID-19 [30]. Therefore, considering the essential role of IgE in allergies, and their relationship with viral infections, it is crucial to study its role in COVID-19 infection [31]. Indeed, *in vitro* studies have shown that the production of specific IgE for different viruses and the ability of IgE to suppress some viruses indicate an important role of IgE/or specific IgE expression against the virus in viral pathogenesis [32]. One of the most important classes of allergy is asthma, and the risk of developing asthma increases with recurrent respiratory infections [33]. For example, the development of asthma after respiratory syncytial virus (RSV) bronchiolitis has been reported in case–control studies. However, the determinants of asthma after RSV and its mechanisms are not clearly known yet [34]. The effect of RSV-specific IgE antibodies in the pathophysiology of virus-induced airway dysfunction has been assessed in a mouse model. The results of this study suggest that RSV-specific IgE may contribute to the pathophysiology of airway dysfunction in children who develop this class of specific antibodies [35]. Moreover, data from recent mouse models suggest that the development of asthma following a severe respiratory viral infection may be arise through the production of antiviral IgE. Hence, this new paradigm helps to find and developing future therapies to prevent or improving atopic disease after the virus [36]. Thus, IgE might represent a new marker for human viral diseases, and IgE may also play a functional role in the pathogenesis of the viral diseases [37,38].

IgE, and COVID-19 in asthma patients

Acute exacerbation of asthma (as in patients with high IgE) cause increased morbidity and health care costs. Since respiratory viral infections can exacerbate asthma [39,40], the symptoms of SARS-CoV-2 infection may be more severe in patients with asthma. However, existing studies have not shown the expected prevalence in asthma patients among patients with COVID-19 [41]. Some aspects of the type-2 immune response, including type-2 cytokines (IL-4, IL-13, etc.) and eosinophil accumulation, may provide potential protective effects against COVID-19 [42,43]. In particular, it has been reported that blood eosinopenia is observed in more than half of acute COVID-19 patients, both in severe and less severe cases. Normalization of eosinophil counts showed improvement in clinical status in a number of other cases [44]. Eosinopenia has been shown to be inversely related to inflammatory markers and can be associated with the severity of COVID-19 [45]. For this reason, in many clinical studies, asthma has not yet been identified as a risk factor for severe outcomes in COVID-19 [46]. On the other hand, asthma and influenza are separate diseases in terms of immunity. Examination of B cell responses in mice with asthma and infected with influenza virus showed that allergic response and airway inflammation were the predominant responses. However, virus-specific IgE antibodies have also been induced by the B cells that mentioned above [47]. So far, it seems that higher levels of IgE are an advantage for protecting against SARS-CoV-2. However, it should be noted that apparent protective effects related to higher expression of IgE in asthmatic patients is the result of the higher activity of their humoral immune system rather than higher levels of IgE. Because, increasing in IgE expression can leads to exacerbation of various syndromes [48]. On the other hand, the flu vaccine also causes IgE sensitivity in young children, which may make them more susceptible to vaccine-induced anaphylaxis. This was rarely seen after vaccination in the H1N1 flu epidemic. This can impose a major challenge for vaccine design and use for this disease [49,50]. In addition, incomplete production of IFNs by pDC and epithelial cells have been observed in severely atopic patients with delayed and ineffective antiviral defenses. Also, IFNs act as negative

regulators of Th2 evolution, differentiation, and function. There is also a negative association between IgE and IFN-α, because IgE cross-linking reduces Toll-like receptor (TLR) 9 expression and TLR-7 signaling, that inhibit the production of type I and III INF from pDCs [51]. One of the attractive goals that can completely change the prognosis of COVID-19 patients is disrupting the activation process of mast cells. Numerous studies provide documentary evidence of the importance of mast cell involvement in the pathogenesis and progression of COVID-19. This occurs by completing the inflammatory process by creating a proper niche of anti-inflammatory cytokines in the infected tissue. Mast cell activation also occurs with the help of IgE; so, it seems that IgE blockade helps to treat patients with COVID-19 [52].

COVID-19, omalizumab and other anti IgE drugs

Omalizumab is a recombinant human anti-IgE antibody originally designed to reduce sensitivity to allergens, and blocks IgE binding to the high-affinity IgE receptor (FcεRI). It also inhibits FcεRI -associated with activation in mast cells by removing surface IgE. Omalizumab prevents IgE and IgE/anti-IgE-dependent degranulation, as well as receptor expression which is done by human mast cells. Additionally, omalizumab can even detach IgE pre-bound to sensitized mast cells. As a result, their response to FcεRI-dependent signals is reduced. These data suggest that omalizumab is an effective inhibitor of sensitized and insensitive mast cells [53] (Figure 1). Defects in cellular antiviral responses is one of the mechanisms that link viral infections to exacerbations of atopic disease. For example, the stimulation of the FcεRI has been shown to inhibit influenza-induced IFN-α secretion. Hence, it has been reported that a decrease in serum IgE by using omalizumab in allergic patients with asthma can reverse the *ex vivo* antiviral responses to IFN-α and improve clinical outcomes. Allergic stimulation through IgE-dependent binding affects the functions of monocyte apoptosis, cytokine secretion, and phagocytosis. Thus, defining the effects of IgE on monocyte antiviral responses could reveal pathways involved in the pathogenesis of atopic disease. The proposed mechanism is that allergic stimulation significantly disrupts the rearrangement of proteins essential for antigen delivery. As a result, stimulation of T lymphocytes is weaker and TH1 antiviral responses are reduced. Also, considering, the association of IgE effects that inhibit virus-induced TH1 can be expressed. Thus, IgE-regulated degradation of antiviral responses in human monocytes might suppress the maturation of virus-induced monocytes and TH1 differentiation (Figure 1). All mentioned above highlights our knowledge about variation of allergen-related pathways in host antiviral responses and indicates the role of monocytes in exacerbations of virus-associated allergic disease [54]. Meanwhile, therapeutic role of IgE blocking drugs in RSV viral infection has already been well established [55,56]. For example, in a clinical trial in children with allergic asthma, treatment with omalizumab reduced the duration of RSV infection, viral shedding, and reduced the risk of developing RSV. These findings provide direct evidence that the IgE blockade reduces the susceptibility to RSV infection and disease [57]. While IgE is involved at the beginning of the inflammatory cascade and can be supposed of as the cause of allergic asthma, eosinophilia can be considered a consequence of the whole process [58]. A case study of a 52-year-old man during COVID-19 with severe allergic asthma treated with omalizumab was also reported, which no evidence of exacerbation of asthma or loss of asthma control or pneumonia was reported. Therefore, IgE-targeting antibodies may have protective effects against viruses in COVID-19 [59]. While corticosteroids reduce in-hospital mortality [60], the drugs are highly immunosuppressive, increasing the risk of bacterial superinfection and resistance to neuromuscular blocking agents, which are widely used in mechanical ventilation in patients with SARS [28]. As a result, an attempt has been made to use corticosteroids by the inhalation method to apply it, and reduce the using dose to prevent its side effects [61]. Thus, IgE blockade might be able to prevent the adverse effects of corticosteroids, which target the entire immune system, and might better balance corticosteroid-induced immunosuppression such that the immune system's response to the virus or other infections remains intact. In fact, corticosteroids have a function similar to omalizumab. Prednisolone at a dose of 1 mg/kg can reduce IgE in patients with asthma with or without pulmonary aspergillosis [62]. However, IgE induces heparin secretion, which is one of the common anticoagulants to neutralize the coagulation effect of Coronavirus. Therefore, the use of IgE blocking drugs should be used with caution, and heparin or another anticoagulant should be adjusted with it [63]. IgE blockers can be utilized as a type of immunotherapy along with conventional drugs in order to cure COVID-19 patients, although this treatment still under investigation [64]. The positive effects of biologic drugs have been proven well for patients with severe asthma. Even in patients who have not been cured with other therapies, biological dugs have shown significant results. Currently, available biological drugs are available as adjunctive therapy for patients with severe asthma included Omalizumab, Mepolizumab, Benralizumab, Reslizumab, and Dupilumab. These biological drugs target type-2 inflammatory pathways and are effective in reducing exacerbation, controlling asthma symptoms, and leading to reduce the use of systemic steroids [65]. Among these, Omalizumab is better known. Because not only it has been shown to reduce inflammation of the nasal mucosa and improve nasal breathing, but it has also been shown to improve nasal sinus function in patients with chronic rhinosinusitis. This mechanism is essential for the initial fight against COVID-19. Also, it can be used to treat patients with a variety of mast cell disorders, even in small doses. Moreover, its usage reduces the spread of the virus due to proinflammatory mediators and the risk of subsequent serious complications in COVID-19 patients. Furthermore, the drug not only has an anti-IgE effect, but also has an inhibitory effect on inflammatory cells such as neutrophils. Also, considering that the over-synthesis of inflammatory cytokines such as IL-6, IL-1β and tumor necrosis factor (TNF)-α are

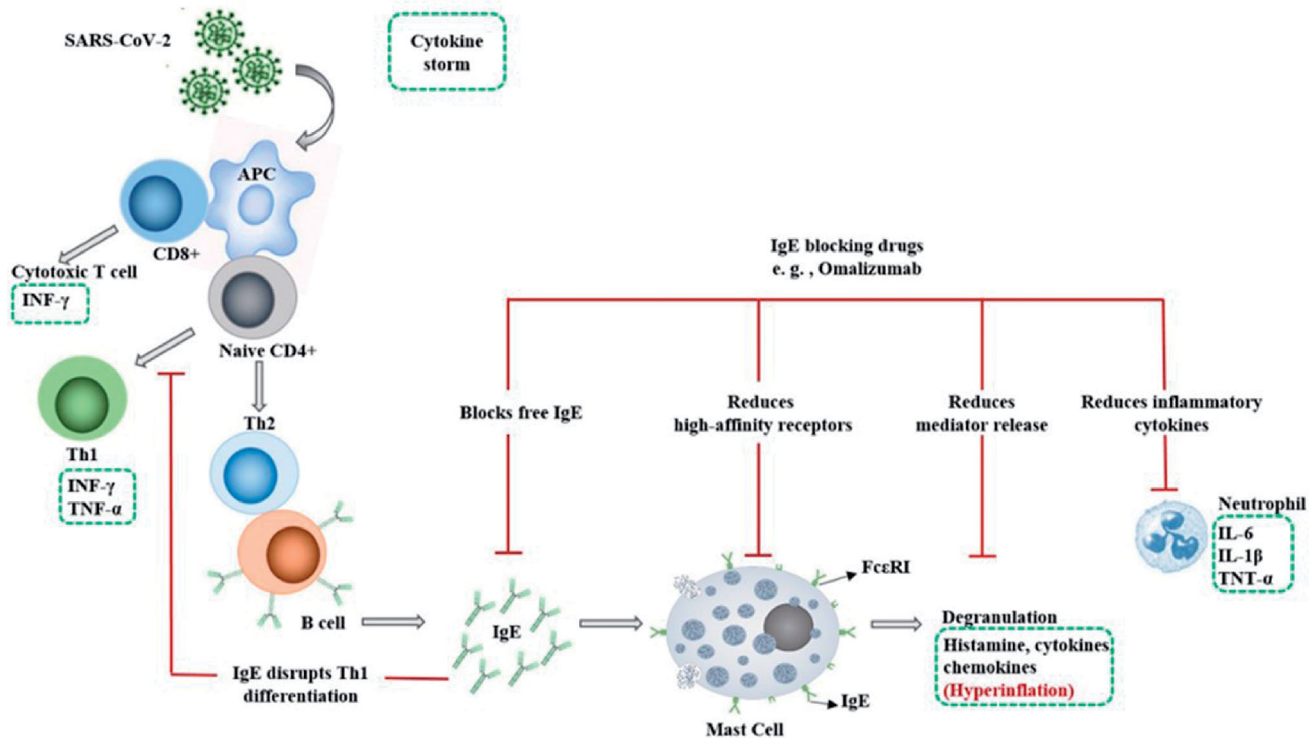

Figure 1. The role of IgE in SARS-CoV-2 induced cytokine storm and IgE blocking drugs (e.g. omalizumab) during immune response.

caused by active neutrophils. It can be concluded that Anti-IgE monoclonal antibodies based drugs can have a significant effect in inhibiting further inflammation and preventing cytokine storm [66] (Figure 1). Also, analyzing preliminary data in a clinical study demonstrated that tocilizumab significantly improved the clinical outcome in severe and critical COVID-19 patients immediately, and it is an effective treatment to reduce mortality in COVID-19 [67].

Conclusion

One of the leading causes of death from COVID-19 is inflammation and severe allergies caused by the virus. Among them, IgE is one of the most important components of sensitivity. Also, production of specific IgE for different viruses and its important role in post-infection allergies by activating mast cells, as well as its function in inhibiting TNF-α activity dysregulated immune response showing an important role IgE is involved in the exacerbation of viral diseases. Therefore, the use of IgE suppressors can improve the symptoms and reduce the severity of the disease in patients. Therefore, it can be concluded that more attention to IgE and further research on its role in COVID-19 infection and other similar viral diseases can create new horizons in the treatment of viral infections.

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