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Therapeutic Monoclonal Antibodies Targeting Cytokine Storm: Inclusion as a Future Treatment for the Severe Cases of COVID-19

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Abstract

Clinical studies have manifested immunotherapeutics as the most propitious for the management of COVID-19 so far. However, the springing up variants of SARS CoV-2 has positioned the role of preventive immunotherapeutics – vaccines in doubt. Even so therapeutic monoclonal antibodies, Tocilizumab – an IL-6 inhibitor and Ravulizumab – a complement protein C5a blocker which are in clinical trial phase –IV are ascertained to be effectual for the COVID-19 cytokine storm and are envisioned to be included as an approved treatment for the severe COVID-19 cases.

Keywords: COVID-19; SARS-CoV-2; Cytokine Storm; Therapeutic monoclonal antibody

Description

Immunotherapy has proven to be the most effective against treating the zoonotic outbreak of Coronavirus disease 2019 (COVID-19) in the form of vaccines, convalescent plasma and treatment therapy based on monoclonal antibody. Vaccine is considered to be the preventive measure against the disease while convalescent plasma and therapeutic monoclonal antibodies are curative measures. Clinical evidences are indicating cytokine storm as still the leading cause of mortality in the patients suffering from COVID-19 regardless of emergent variants of SARS CoV-2 which brought about it. Cytokine storm is characterized by elevated levels of proinflammatory cytokines [1-3]. Till 25 April, 2021 more than 5000 clinical studies are listed for COVID-19 in the database of clinical trials.gov. Out of them around 100 studies are intervening therapeutic monoclonal antibodies targeting interleukins (IL-6, IL-1ra, IL-8, IL-1β, IL-17A, IL-33), interferon-gamma, tumor necrosis factor-alpha, P- selectin, connective tissue growth factor, plasma kallikrein, tumor necrosis factor superfamily 14, granulocyte macrophage colony stimulating factor, colony stimulating factor 1 receptor, C-C chemokine receptor type 5, cluster of differentiation 14 and 147, vascular endothelial growth factor, programmed cell death protein-1, Angiopoietin - 2, human factor XIIa, complementary protein 5, natural killer cell receptor G2A, human epidermal growth factor receptor 2, immunoglobulin-like transcript 7 receptor, complement component fragment 5a receptor and viral attachment to the human cell as a potential treatment for the of severely ill patients of COVID-19. Amongst all, three studies on Tocilizumab – an IL-6 inhibitor, one study on Ravulizumab – a complement protein C5a blocker and three studies on Bamlanivimab – a recombinant humanized mAb that binds to the receptor binding domain of the spike protein of virus and blocks its attachment with human ACE 2 receptor are in clinical phase IV which featuring them to be an approved treatment for the severe cases of COVID- 19.

Tocilizumab a recombinant humanized Immunoglobulin (Ig) G1 monoclonal antibody that inhibits the binding of IL-6 to the soluble and membrane-bound forms of the IL-6R is trialed alone or in combination with other antiviral drugs for managing the upstaged COVID-19 associated cytokine storm as summarised in Table 1. During the pathogenesis of cytokine storm, the augmented level of IL-6 along with other proinflammatory cytokines has been observed and is considered to be the primary reason for the mortality associated with COVID -19. In view of this, three clinical studies are in phase IV to conclude that intravenous administration of Tocilizumab at a dose of 8 mg/kg reduces serum IL-6 level and rapidly improve clinical manifestations of COVID-19 pneumonia.

Another humanized monoclonal antibody under the clinical trial phase –IV is Ravulizumab which pharmacologically approached to target the dyregulated immune response that drives the multi organ damage during the severe phase of COVID-19. It is evidential that in cytokine storm, proinflammatory cytokines especially IL-2, IL-6 and TNF-α which are spearheading the tissue injury found in high concentration. Complement system is a key contributor to the generation of these proinflammatory mediators. Ravulizumab complexes with complement protein C5 and prevents its cleavage to C5a and C5b. C5a mediate complement actions including inflammation, platelet activation, endothelial cell activation, coagulation and leukocyte recruitment are observed predominantly in COVID-19 [4]. Clinical trial Phase –IV entitled as TACTIC-R is conducted in United Kingdom with an objective to investigate the efficacy of intravenously administered. Ravulizumab as paramount treatment that hampering the progression of SARS CoV-2 infection and reduces the incidence of multiorgan damage associated with cytokine storm. When the world is still struggling to combat the pandemic, genomic modification and evolution of SARS Cov-2 variants B.1.1.7, B.1.351, B.1.1.248 and B.1.249 has put the preventive and curative course of action of ancestral SARS Cov-2 in the dock. Mutations dominating in the viral spike glycoprotein impact the efficacy of vaccines and neutralizing therapies. Evidences indicates that a subset of neutralizing clinical candidates to the receptor binding domain of spike are less effective against these variants especially the highly infectious UK variant B.1.1.7. However,

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Name of Therapeutic MABs	Mechanism of action	Title of study	Registration NO	Country	Current status	Link	Entered	Last update posted date
Complete Response (CR)	Complete Response (CR)	TOCILIZUMAB- An option for patients with COVID-19 associated	NCT04730323	Pakistan	Completed	https://clinicaltrials.gov/ct2/show/NCT04730323	January 29,2021	January 29, 2021
		The use of Tocilizumab in the management of patients who have severe COVID- 19 With suspected pulmonary hyperinflammation	NCT04377750	Israel	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04730323	May 6, 2020	May 6, 2020
		Comparative therapeutic efficacy and safety of different antiviral and anti inflammatory drugs in COVID-19 patients	NCT04779047	Egypt	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04779047	March 3, 2021	March 7, 2021
Ravulizumab	Complement Protein C5a blocker.	mulTi-arm therapeutic study in Pre-ICu patients admitted with Covid-19 - repurposed drugs (TACTIC-R) (TACTIC-R)	NCT04390464	United Kingdom	Recruiting	https://clinicaltrials.gov/ct2/show/NCT04390464	May 15, 2020	

Table 1: Promising therapeutic monoclonal antibodies under the clinical trial phase –IV.

these mutations are not escalating the disease severity in spite of higher virus loads in the respiratory secretions. Hence, the therapeutic mAbs – Tocilizumab and Ravulizumab are still found optimistic treatment against the cytokine storm associated with SARS Cov-2 infection irrespective of its accountable variants [5,6].

Conclusion

From the above discussion, it is needless to say that therapeutic monoclonal antibodies like Tocilizumab and Ravulizumab can be the triumphant therapy to win the battle against progression of COVID-19 infection across the globe in line to their promising performance in clinical trial phase-I, II and III.

Conflict of interests

There is no conflict of interest to disclose

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