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Review Article

IMPLICATION OF MONOCLONAL ANTIBODY FOR COVID-19 TREATMENT

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ABSTRACT

Coronavirus induced disease-19 (COVID-19) pandemic affecting entire world has continued to pose threat despite nearly a year of its onset. With more than 50 vaccine candidates targeting COVID-19 on trials and 15 at the final stage of testing, wide availability to the general public is still a long way to go. Thus alternative therapeutics is in the progress to minimize the effect of COVID-19. This systematic review evaluated the articles related to immunotherapy for COVID-19. PubMed database was used to search for keywords; COVID-19, immunotherapy, and monoclonal antibody for relevant publications of the year 2020. The review was performed based on PRISMA protocol and the final 20 articles were included in the final review. These studies demonstrated that Tocilizumab, the monoclonal antibody that blocks IL-6 receptors has improved outcome in COVID-19 infected patients.

Keywords: Immunotherapy, Monoclonal antibody, PRISMA, SARS-CoV-2, Tocilizumab.

INTRODUCTION

The pandemic of Corona Virus Induced Disease-2019 (COVID-19) outbreak caused by Severe Acute Respiratory Syndrome Corona virus 2 (SARS-CoV-2) has claimed over 1.7 million lives with more than 76 million infected globally (WHO, 2020). This highly contagious disease spread by the respiratory droplets of infected person and has expanded across the world due to high transmission rate. Compared to the closely related beta coronaviruses, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), transmission rate in SARS-CoV-2 is relatively high with large fraction contributed by asymptomatic carriers (Al-Tawfiq & Gautret, 2019; Wilder-Smith *et al*., 2005). The disease induced by SARS-CoV-2 range from asymptomatic, noted without any signs and symptoms to symptomatic mild phase involving upper airway and/or severe lethal state infiltrating the lungs with progression to acute respiratory distress syndrome (ARDS) (Asadi *et al.*, 2020; Shi *et al*., 2020).

The main cause of death in COVID-19 infected patient is ARDS, which is associated with uncontrolled inflammatory response resulting from the release of pro-inflammatory cytokines and chemokines- the cytokine storm (Li *et al*., 2020). Patients with COVID-19 have increased plasma concentration of inflammatory cytokines, such as Interleukins (IL), and over expression of tumor necrosis factor α (TNF α), granulocyte macrophagy-colony stimulating factors (GM-CSF), monocyte chemoattractant protein1, macrophage inflammatory protein 1 alpha, and interferon-γ-inducible protein 10 (Rothan *et al*., 2020). Cytokine release syndrome has been suggested to hinder the adaptive immune response against SARS-CoV-2 infection contributing to the severity of the disease (Li *et al*., 2020).

Containment of COVID-19 has also been challenged by an ambiguous pathogenesis mechanism. This has lead to an uncertainty in the therapeutics specifically targeting SARS-CoV-2. The recently introduced vaccines approved after the third phase of trial are yet to be assessed. Immunotherapy has been an efficient option considering its successful use against the closely related viruses SARS-CoV and MERS-CoV. Thus the purpose of this article is to review the use of monoclonal antibody, as an immunotherapeutic against novel corona virus SARS-CoV-2 to ameliorate the condition of patient.

METHODS

Search strategy

A systematic literature review was performed to summarize information on monoclonal antibody therapeutics for COVID-19 following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

A literature search was conducted using PubMed database for keywords such as, COVID-19, immunotherapy, monoclonal antibody, and related words. The search included published articles for the year 2020. Title and abstracts were reviewed to detect the related articles. Articles that have mentioned about immunotherapy for COVID-19 were selected. The articles with only abstract were excluded. Similarly articles that did not mention about the immunotherapeutic for the treatment of infection due to SARS-CoV-2 but only SARS, MERS, other viruses and ailments were excluded. The full texts of the relevant articles were read to decide on whether they could be included.

Data extraction and presentation

Data from the articles were extracted after reading the articles which were presented in the tables as summary. This review addressed six domains: drug name, target site, route of administration, outcome of treatment, authors, and article type.

RESULTS

A total of 164 non-duplicate potentially eligible articles were retrieved from the database search. The review articles and experiment protocols were not considered so 37 such articles were excluded in the initial search. Then from the remaining 127 articles, 59 were excluded after full text screen since full text could not be retrieved for some while others were not related to monoclonal antibody therapeutics. Finally 48 articles without data on SARS-CoV-2, but rather MERS, SARS, cancer and arthritis were excluded. A total of 20 articles were included in the final review (Fig. 1).

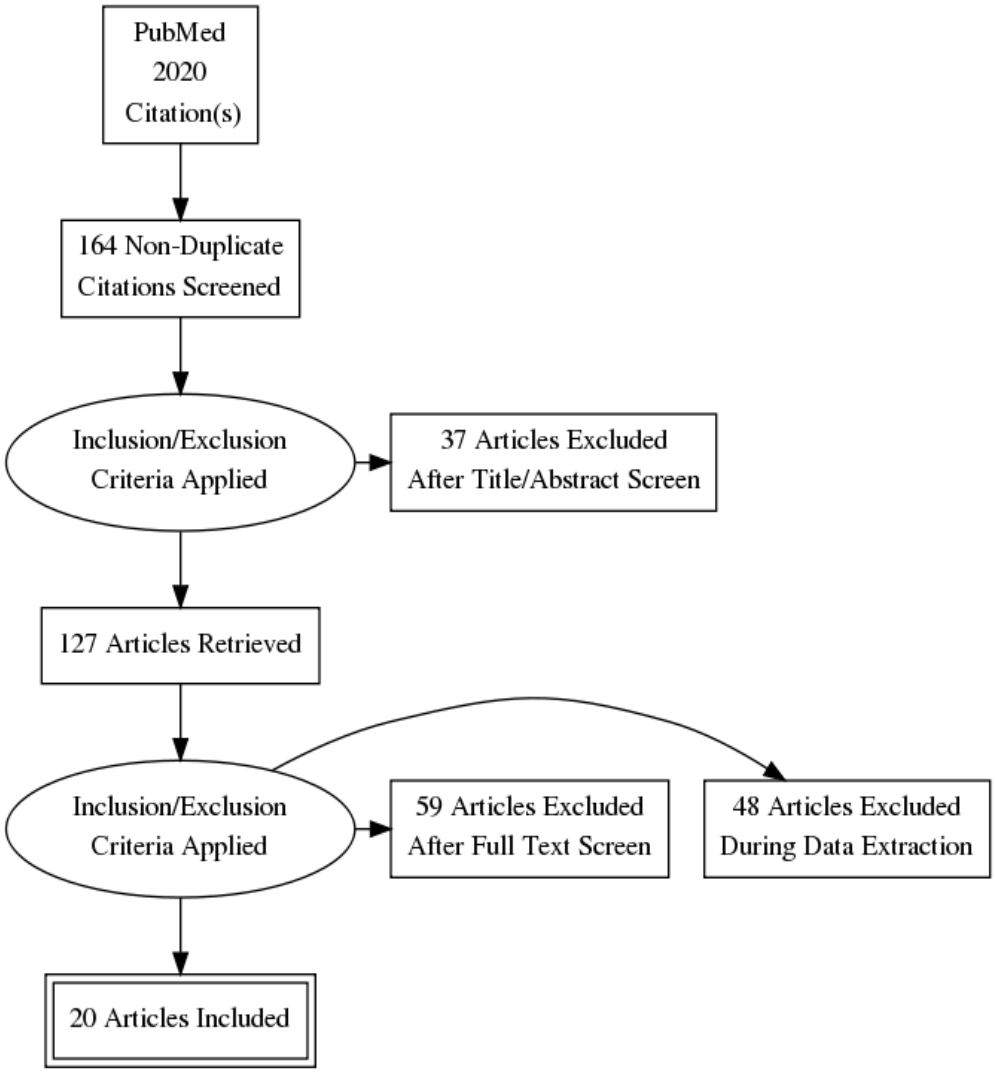

Fig. 1. The article search flow chart

From the extracted data, humanized monoclonal antibody used for SARS-CoV-2 incorporated were Tocilizumab, Sarilumab, Itolizumab, Siltuximab, Infliximab and Lenzilumab. The monoclonal antibodies that target interleukin-6 receptor included in Table 1 are Tocilizumab and Sarilumab. They are administered intravenously, although some have been introduced subcutaneously into the patient (Hassoun *et al*., 2020; Montesarchio *et al*., 2020). Recovery in the patient with marked decreased C-reactive protein (CRP) level in blood and improvement in inflammatory markers with reduced fever were the commonly observed features in the patient treated with these interleukin-6 receptor blockers. The recovery time however varied with the authors. The improvement period ranged from 5 days to two weeks as mentioned in most of the literature. Substantial research articles available on

Tocilizumab treatment demonstrated faster recovery compared to Sarilumab.

Table 1. Overview of interleukin 6 receptor target monoclonal antibody for COVID-19 treatment

Drug name	Target site	Route of administration	Outcome of treatment	Author	Article type
Tocilizumab	Interleukin 6 receptor		CRP decreased significantly, IL6 elevated at beginning then decreased afterwards	Luo *et al.* (2020)	Research
			CRP decreased within 2-6 days. IL6 was not detected	Di Giambenedetto *et al*. (2020)	Research
		Subcutaneous	Improvement in inflammatory markers within 7 days, improvement in clinical syndrome	Hassoun *et al.* (2020)	Research
		Intravenous	CRP decreased significantly, fever normal after 1 day	Xu *et al.* (2020)	Research
		Intravenous	CRP decreased, fever reduced, peripheral lymphocyte increased	Zhao (2020)	Research
		Intravenous	CRP decreased, fever reduced, radiological improvement	Alattar *et al.* (2020)	
			Temp returned to normal quickly after treatment, 20 out of 21 patients discharged after 2 weeks, no adverse effect,	Fu *et al*. (2020)	Commentary
Sarilumab		Intravenous	89.7 % patients improved in 19 days,	Gremese *et al*. (2020)	Research
		Subcutaneous	CRP level decreased, mostly below upper normal range within 5 days	Montesarchio *et al*. (2020)	Report
		Intravenous	CRP normalized in 6 days compared to 12 days in control group	Della-Torre *et al.* (2020)	Report
			Partial improvement	Caballero Bermejo *et al.* (2020)	Trial

The anti-CD6 monoclonal antibody, Itolizumab, decreased the level of IL-6 in the serum within 48 hours of intravenous administration (Table 2). Similarly, Siltuximab, which directly binds Interleukin-6 delayed normalization of IL-6 compared to Tocilizumab when administered subcutaneous. Reduction of CRP in 76 % patient with 33 % clinical improvement was reported in a research (Table 2). Similarly, a case study reported an improvement in cytokine level in serum with decreased IL6 and IL8 when Infliximab, the TNF alpha target was administered intravenous. Lenzilumab, the granulocyte-monocyte colony stimulating factor (GM-CSF) target, did not improve the symptoms within 24 hours of intravenous administration (Melody *et al.*, 2020) but improvement in CRP and inflammatory cytokines was reported in other study (Temesgen *et al*., 2020).

Table 2. Overview of monoclonal antibody with different target site for COVID-19 treatment

Drug name	Target site	Route of administration	Outcome of treatment	Author	Article type
Itolizumab	CD6 receptor	Intravenous	Anticipated in treating cytokine storm, anti-inflammatory	Loganathan *et al.* (2020)	Trial
		Intravenous	Circulating IL6 decreased within 48 hrs.	Diaz *et al.* (2020)	Research
		Intravenous	Serum IL6 decreased after 48 hrs	Atal *et al.* (2020)	Research
		Intravenous	IL6 decreased after 1 dose in 48 hours	Saavedra *et al.* (2020)	Research
Siltuximab	Interleukin-6	Subcutaneous	Delayed normalization of IL6 compared to Tocilizumab	Palanques Pastor *et al.*	Report
		Intravenous	CRP reduced in 76% patient, Clinical improvement in 33%	Gritti *et al.* (2020)	Research
Infliximab	TNF-alpha	Intravenous	Cytokine improved, normalization of TNF alpha, decreased IL6 and IL8	Dolinger *et al.* (2020)	Case study
Lenzilumab	Granulocyte-monocyte colony stimulating factor	Intravenous	Symptom did not improve but 24 hours after administration of Tocilizumab improvement in CRP and Interleukins	Melody *et al.* (2020)	Case study
		Intravenous	Clinical improvement in treated patient in 5 days compared to 12 days in non-treated control; reduced inflammatory myeloid cells in 2 days, Improvement in CRP and inflammatory cytokines	Temesgen *et al.* (2020)	

DISCUSSION

Attachment and entry into the host cell is the primary strategy exploited by virus and other pathogens in the process of infection. Therapeutics to block the attachment and entry are promising approach in thwarting the pathogenesis mechanism elicited by the virus. Monoclonal antibodies that recognize different epitopes on the viral surface have been effective immunotherapy owing to their specificity, purity and safety.

A characteristic feature in COVID-19 being cytokine storms induced by virus, immunotherapy targeting the cytokines can help ameliorate the condition. IL-6 is considered a key cytokine in COVID-19 due to its elevation correlated with the severity induced by cytokine storm (Crisafulli *et al.*, 2020; Damas *et al.*, 1992). An approach for the treatment of rheumatoid arthritis by blocking IL-6 receptor has been a strategy adopted to calm the inflammatory storm with the use of Tocilizumab (Alfonso-Cristancho *et al*., 2017; Fu *et al.*, 2020).

Tocilizumab and Sarilumab, target and antagonize both membrane-bound and soluble IL-6 receptor. The food and drug administration (FDA) approved Tocilizumab has been reported with the promising preliminary clinical results from clinical trials and devoid adverse reaction (Fu *et al.*, 2020). Improvement in the symptoms of patient followed by switching to the use of Tocilizumab was evident when the previously used Lenzilumab did not show any progress (Melody *et al*., 2020). Gradual decrease in IL-6 level in patient treated with Tocilizumab due to inhibition of inflammatory activity and improvement in clinical outcome has been reported (Hassoun *et al*., 2020; Luo *et al*., 2020). Sarilumab was used in Italy to treat patients with severe SARS-CoV-2 pneumonia (Della-Torre *et al*., 2020) and in China as an alternative anti-IL-6 receptor during the shortage of Tocilizmab (Gremese *et al*., 2020). Available in both intravenous and subcutaneous formulation, it was effective with good clinical outcome and do not present adverse effect (Della-Torre *et al*., 2020; Gremese *et al*., 2020).

A CD6 receptor target, Itolizumab reduce the activation, proliferation, and differentiation of T cells into pathogenic effector T cells leading to a decrease in production of proinflammatory cytokine (Nair *et al*., 2010). This drug has been approved in India for psoriasis treatment and is used for COVID-19 patients with moderate to severe ARDS (Longanathan *et al*., 2020). Unike Tocilizumab and Sarilumab, the IL-6 target drug Siltuximab have affinity with IL-6. Though the efficacy of Siltuximab has been reported to be identical to Tocilizumab, it has produced a delayed normalization of IL-6 levels compared to the latter (Palanques-Pastor *et al*., 2020).

In a case study, involving a patient with Crohn's disease who was suspected with COVID-19, Infliximab was administered to co-manage both entities (Dolinger *et al*., 2020). Since the inflammatory disease overlapped, the real picture of cytokine storm induced by SARS-CoV-2 was not confirmed in that study. Thus they recommended further investigation for implication in COVID-19. Improvement in inflammatory markers with patient treated with Lenzilumab, the GM-CSF target, has been reported (Temesgen *et al*., 2020). However, randomized control clinical trial needs to validate the outcome of the treatment. A case study has asserted the superiority of Tocilizumab over Lenzilumab in the management of cytokine mediated syndrome (Melody *et al*., 2020).

CONCLUSION

Considering all the evidences from the selected articles reviewed, Tocilizumab continues to be the most effective among the currently introduced monoclonal antibody therapeutics for the improvement of clinical outcomes in COVID-19 infected patients.

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