A Review Study on Efficacy of Immunomodulatory agents used for the Treatment of Covid-19

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ABSTRACT

The infection started at December, 2019 with the random elevation of respiratory tract disorders at Wuhan hospital in China. Sequencing of lower respiratory tract samples by independent laboratories in China identified a novel corona virus distinct from the other Severe Acute respiratory Syndrome (SARS) strains of coronavirus previously known to infect humans, which was earlier named as Corona Virus Disease 2019 (COVID-19) by the world health organization. The present review work highlighted the outbreaks of COVID-19 on the basis of scientific journals published in the reputed research articles and other authentic sources. Increased morbidity and mortality rate in COVID-19 is largely associated with Acute Respiratory Distress Syndrome (ARDS). Throughout the period of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) infections and SARS CoV-2, Elevated level of proinflammatory cytokines and chemokine was commonly observed in patients requiring Intensive Care Unit (ICU) admission as compared to those in which the infection was less severe and did not require ICU admission due to excessive immune responses induced by the immune system. Potential of immunomodulatory agents such as Interleukin- 1 (IL-1) and Interleukin-6 (IL-6) receptor antagonist, Tumor Necrosis Factor- α (TNF- α) blockers and corticosteroids in treatment of COVID-19 declared urgent need for clinical researches to precisely confirm the effectiveness and safety of the therapeutics.

Key words: SARS-CoV-2, Covid-19, Cytokines, Corona Viruses and Immunotherapyy.

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INTRODUCTION

Wuhan Hospital in China reported for the first time a respiratory tract disorder in December, 2019. This unknown cause of infection has responsible to cause various symptoms such as immunodeficiency, fever, sneezing, cough and breathlessness. Most of the initially identified patients were geographically linked to a local wet seafood wholesale market, where living or slaughtered wild animals are sold. Sequencing of lower respiratory tract samples identified a novel coronavirus distinct from the other SARS strains of coronavirus previously known to infect humans. The World Health Organization (WHO) subsequently identified this infective virus as Severe Acute Respiratory Syndrome-Corona Virus-2 (SARS-Cov-2) and declares it as a highly contagious virus which is rapidly transmitted among humans by either respiratory, aerosol or contact transmission. As a result, WHO officially named the 2019 novel coronavirus as COVID-19 on 7th January, 2020. The virus continue to spread rapidly to over 200 countries and territories, resulting in 13,885,746 confirmed cases, 7,779,604 recovered and 592,573 deaths globally according to a database of John Hopkins University as of 17th July 2020.[1-3]

The *Coronaviruses* genus is a member of the *Coronaviridae* family, and has medium-sized enveloped positive-stranded RNA viruses whose name derives from their characteristic crown-like appearance in electron micrographs.[4,5] The Corona viruses are widely known for their large RNA genomic structure. The corona virus genome is 27-32 kb long and mainly replicates using a nested set of messenger ribonucleic acids

mRNAs.[6] In the light of previous reports, it was successfully identified reported that first coronavirus was identified in chickens in the 1930s and in 1960s the virus was time found to infect humans.[7] The mutation in the genome and surface proteins has been observed in the Corona virus due to the varying host pattern. Till date, the studies have observed seven corona viruses' serotypes which have been associated with different types of pathogenic symptoms. The major identified corona virus serotypes are HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2. Four (229E, OC43, NL63 and HKU1) endemic (generally found among particular set of individuals and mostly result to mild disease, while three (SARS-CoV, SARS-CoV-2 and MERS-CoV) are more fatal leading to severe disease and epidemiologically account for about 10-15% of common colds, mostly during winter.[8]

However, the previous reports of study from china has identified about 15–20% of the patients with COVID-19 have severe diseases with interstitial pneumonia which can be resulted in the development of Acute Respiratory Distress Syndrome (ARDS). The major symptom of *Pneumonia* includes decreased oxygen saturation, with severe bilateral ground glass abnormalities, patchy consolidation and alveolar exudates.[9,10] In patients with ARDS, the virus can induce an excessive and aberrant host immune response characterized by an up regulation of pro-inflammatory cytokines, resembling the clinical and serological features of Cytokine Release Syndrome (CRS).[11]

Viral infection and immune response

Initiation of immune response to an invading microorganism like a virus requires host sensing to organism and its constituents such as uncapped viral RNA, cellular damage and metabolic changes resulting from infection carried out by a germline-encoded Pattern Recognition Receptors (PPRs).[12]

In a normal immune response, immune system secretes variety of cells and chemical messengers in a complex order, resulting to localized inflammatory state. Interaction of vegetal cells with pathogen associated molecular pattern trigger immune reaction which attract different immune cells to the site of infection such as macrophages, monocytes and natural killer (NK) cells leading to release of low molecular weight signalling proteins specifically interleukin 1β, Interleukin-6 and Tumour necrosis factor α as show in Figure 1.[13,14]

Immune response against SARS CoV-2

The most important factor associated with pathophysiology of SARS-CoV-2 is the host immune response which results due to binding of spike glycoprotein to its receptor Angiotensin Converting Enzyme-2 (ACE-2).[16,17] Cryogenic electron microscopy and surface Plasmon resonance shows the similarities and minor differences between SARS-CoV-2 and SARS S proteins. However, the affinity of SARS-CoV-2 S protein binding to ACE2 is 10 to 20 times higher than that of the SARS S protein; as such SARS COV-2 is transmitted rapidly among humans than SARS COV.[18]

The increased morbidity and mortality rate in COVID-19 is largely associated with Acute Respiratory Distress Syndrome (ARDS). Therefore, it's considered an important clinical condition which results to tremendous consequence in SARS CoV-2.[19] ARDS is most common in clinical complications such as pneumonia, sepsis, pancreatitis and blood transfusion. ARDS is characterised by the increased lung permeability and the exudation of protein-rich pulmonary edema fluid into the airspaces, which ultimately results to respiratory insufficiency and damage in the blood-air barrier (alveolar–capillary membrane).[20]

Elevated level of pro-inflammatory cytokines (eg: Interferon γ, interleukin (IL-) 1B, IL-6, IL-12) and chemokine's (CXCL10, CCL2) is one of the classical feature seen in both SARS and MERS infections. However, in SARS CoV-2 it was realised that patients requiring ICU admission displayed higher concentrations of CXCL10, CCL2 and TNFα as compared to those in which the infection was less severe and did not require an ICU admission.[21,22]

Immunomodulatory agents

- **Interleukin-1 Receptor Antagonist (IL-1-RA)** is a humanized protein by *IL1RN* gene which bind to the cell surface of interleukin-1 receptor (IL-1R), the same receptor that binds interleukin 1 (IL-1), thereby preventing IL-1 signalling as shown in Figure 2.

  Anakinra (ANK) is a non-glycosylated, recombinant form of human IL-1 receptor approved by the Food and Drug Administration (FDA) in 2001, which mainly inhibit binding to the IL-1 receptor and prevent activation of this receptor by either IL-1β or IL-1α Potential role of ANK in the treatment of respiratory dysfunction in COVID-19 patients has been reported, with need
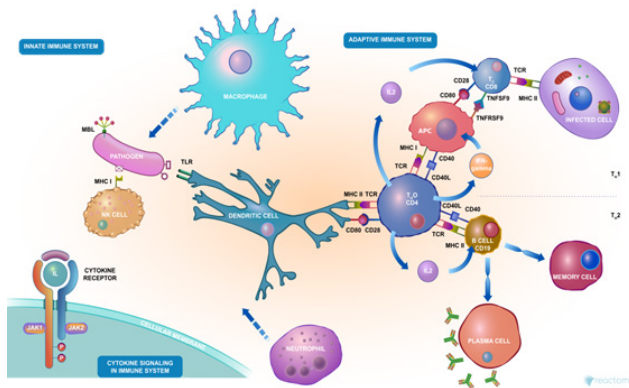
Figure 1: Immune response to viral infection.[15]

Figure 2: Biologic function of IL-1 and mechanism of inhibition by IL-1Ra.[25]

to further investigate the clinical efficacy and safety of this immunomodulatory agent.[23]

In a multi-centre study which examine the clinical efficacy of ANK in 41 patients with refractory Adult-Onset Still's Disease (AOSD), it was realised that ANK yielded rapid and maintained clinical and laboratory improvement in these patients. However, despite the limitations of the study, randomized clinical trials are required to critically elaborate on the effectiveness of IL-1 receptor blockade in AOSD and other disease including COVID-19.[24]

- **Interleukin-6- Receptor Antagonist (IL-6_RA):** are mainly used for the treatment of Rheumatoid Arthritis, Systemic Juvenile Idiopathic Arthritis, Cytokine Release Syndrome and Giant Cell Arthritis.[26,27]

  Tocilizumab also known as atlizumab, is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). Interleukin 6 (IL-6) is a cytokine that plays an important role in immune response; the immunosuppressive drug is widely used for the treatment of rheumatoid arthritis, systemic juvenile idiopathic arthritis and other autoimmune diseases.[28]

  Efficacy and safety of tocilizumab (IL-6RA) was confirmed in 21 patients diagnosed with severe COVID-19. The temperature of all the patients returned to normal, respiratory function improved significantly, 20 patients have been recovered and discharged within 2 weeks after the tocilizumab therapy, 1 patient is recovering. Interestingly, no adverse drug reactions were reported during the treatment with tocilizumab. However, a multicentre, large-scale clinical trial (ChiCTR2000029765) has been launched to further confirm the effectiveness of the treatment.[29]

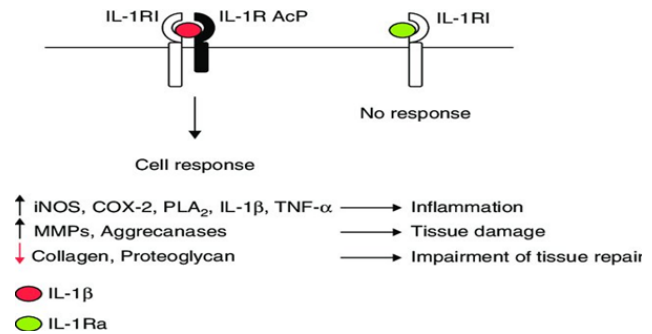 Another study which examined the effectiveness of treatment with tocilizumab shows improvement

in patients diagnosed with severe COVID-19 where Fever returned to normal on the first day and other symptoms improved remarkably within a few days. Within 5days after tocilizumab, 15 of the 20 patients had lowered their oxygen intake and 1 patient needed no oxygen therapy with normal CT scans, decreased percentage lymphocytes in peripheral blood and significant decreased in C reactive protein level.[30]

- **TNF-α blockers** (Tumor Necrosis Factor- α) are type of drugs that suppress immune system by blocking the activity of TNF-α (an important pro-inflammatory cytokinemostly expressed by immune cells and other cells that promote inflammation). Uncontrolled secretion of TNF-α has a pathogenic role in some inflammatory conditions such as Rheumatoid arthritis, psoriatic arthritis, crohn's disease and ankylosing spondylitis.[31]

  Studies in animal models shows that neutralizing the activity of TNFs or blocking their receptors yield a protective strategy and decreases morbidity and mortality rate of induced SARS-CoV.[32]

  A research article shows recovery with regression of fever, cough and myalgia at day 10 along with a decreased CRP level by a subcutaneous administration of TNF-α inhibitor such as etanercept 50 mg and methotrexate 20 mg on 60 years old COVID-19 individual suffering from spondyloarthritis.[33]

- **Corticosteroids** are synthetic drugs which imitate cortisol (steroid hormone produced by adrenal gland) and used for treatment of autoimmune diseases, asthma and skin conditions. They involved wide range of processes in the body, such as regulation of blood pressure, suppressing inflammatory activities, metabolism and bone formation.

  A Systematic review and meta-analysis examining the efficacy and safety of corticosteroids in

COVID-19 patients with ARDs shows a promising result, while the results are inconsistence in patients without ARDs.[34]

On contrary, another systematic review and meta-analysis shows that severe COVID-19 patients more likely require corticosteroids for suppressing immune response, while those with mild and moderate conditions are not recommended for treatment with corticosteroids because corticosteroids could lead to high mortality, longer length of stay, high rate of bacterial infection and hypokalaemia. However, more multicentre clinical trials are needed to further verify this conclusion.[35]

CONCLUSION

The greatest global public health emergencies results due to COVID-19 pandemic called for multiple therapeutic intervention, one of the important dimension is to focus on inflammatory activities and changes at the disease state. The most notable property among, is the prolonged and aberrant release of cytokines in COVID-19 patients which results to ARDS or multiple organ dysfunctions. However, it declared urgent need to accelerate the on-going clinical trials evaluating the safety and effectiveness of immunomodulatory agents widely known to suppress inflammatory responses.

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CONFLICT OF INTEREST

The authors declare that not competing interests exist.

Author contributions

Mr. Abdulaziz Umar Kurya had the original idea of the article, literature search and prepared the original draft. Mr. Abdulhakim Umar Toro and Mr. Usman Rabiu Bello conducted the data analysis, write, review and edit the article. Dr. Dinesh C. Sharma supervised and critically revised the work.

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