Monoclonal Antibodies in COVID…Where do we stand?

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ABSTRACT

COVID-19 19 pandemic has overwhelmed all health care systems globally. As the number of infected populations increased, the mortality also increased. Race to find an ultimate cure to this novel disease began. The antiviral drugs were repurposed and search for antibodies to fight the infection continued.

Monoclonal antibodies are lab-made drugs meant to mimic natural antibodies to SARS-CoV-2, the virus that causes Covid-19. The first step in pathophysiology of SARS-CoV-2 infection is the attachment of Viral spike protein to ACE 2 receptors on the cell, activating the inflammatory cascade and release of various cytokines. The Cytokine storm heralds the severe immunological damage to the body, especially lungs causing severe ARDS, multiorgan failure and death.

Among the few experimental drugs approved for use in COVID 19 infection are monoclonal antibodies like Tocilizumab, Etolizumab and severalof them have been registered in clinical trials. So, are they really effective? When should they be ideally given? What is their efficacy as far as disease progression, requirement of assisted ventilation and mortality is concerned?

A brief review of pathophysiology, mechanism of action and literature for evidence-based analysis of Monoclonal antibodies in COVID-19 has been presented here.

Introduction :

The severe acute respiratory syndrome (SARS) is caused by a novel coronavirus SARS CoV-2 belonging to the family Coronaviridae. The disease caused by this virus, termed coronavirus disease 19 or simply COVID-19, has rapidly spread throughout the world at an alarming pace and has been declared a pandemic by the WHO on March 11, 2020[1].

Pathophysiology :

COVID-19 spreads between people, mainly when an infected person is in close contact with another person. The virus can spread from an infected person's mouth or nose in small liquid particles when they cough, sneeze, speak, sing, or breathe heavily. These liquid particles are of different sizes, ranging from larger 'respiratory droplets' to smaller 'aerosols'. Other people can catch COVID-19 when the virus gets into their mouth, nose, or eyes, which is more likely to happen when people are in direct or close contact (less than 1 meter apart) with an infected person. Current evidence suggests that the main way the virus spreads is by respiratory droplets amongst people who are in close contact with each other[2]. The report in Lancet shows that ARDS is the main death cause of COVID-19. Of the 41 SARS-CoV-2 infected patients admitted in the early stages of the outbreak, six died from ARDS[3,4].

ARDS is the common immunopathological event for SARS-CoV-2, SARS-CoV and MERS-CoV infections. One of the main mechanisms for ARDS is the cytokine storm, the deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines (IFN- , IFN- , IL-1 , IL-6, IL-12, IL-18, IL-33, TNF- , TGF , etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells in SARS-CoV infection. Similar to those with SARS-CoV, individuals with severe MERS-CoV infection showed elevated levels of IL-6, IFN- , and CCL5, CXCL8, CXCL-10 in serum compared to those with the mild-moderate disease. The cytokine storm triggers a violent attack by the immune system to the body,

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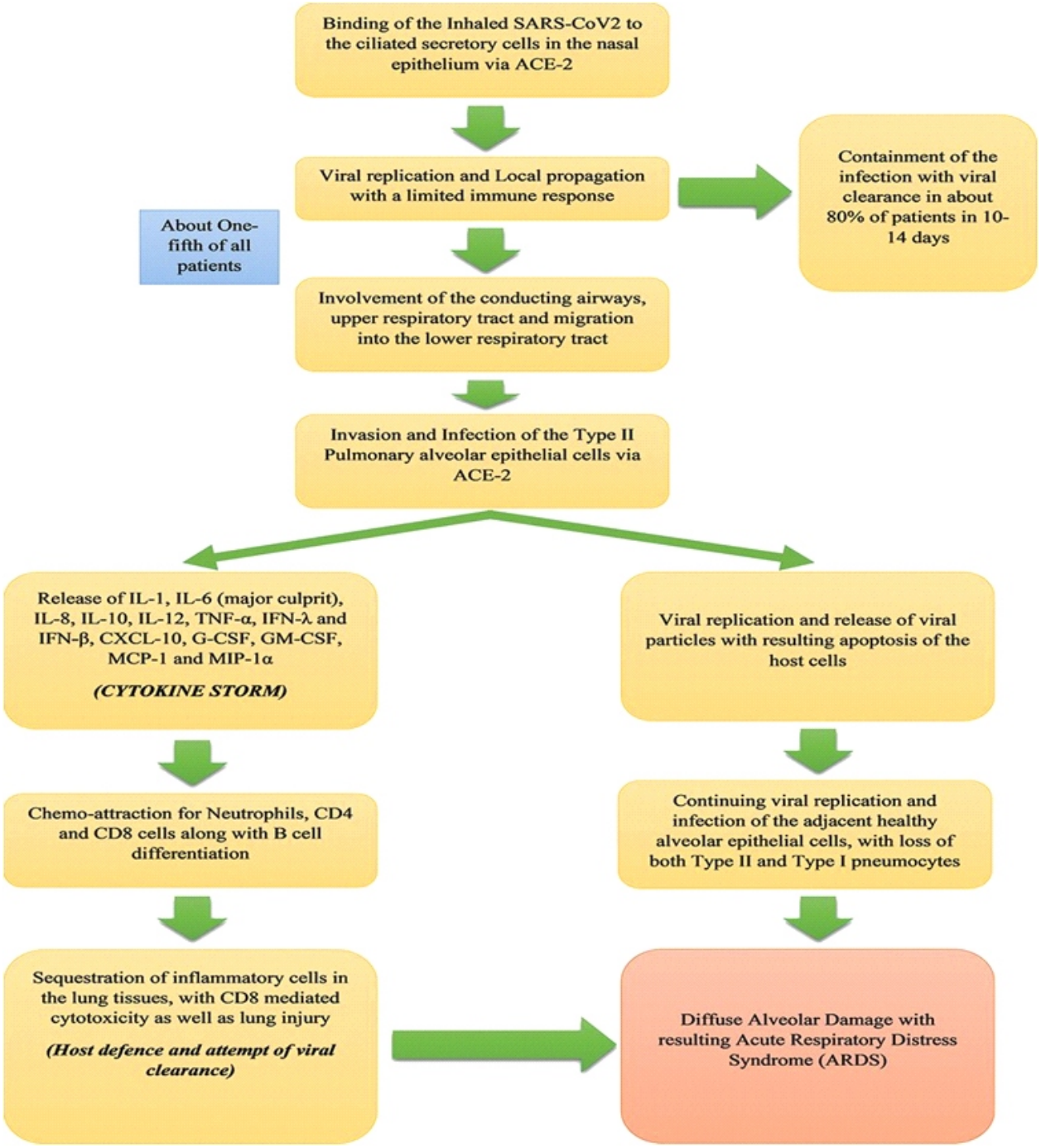
Received on 25th December 2020 Accepted on 30th December 2020

cause ARDS and multiple organ failure, and finally lead to death in severe cases of SARS-CoV-2 infection, just like what occurs in SARS-CoV and MERS-CoV infection[4]. An overview of the disease pathophysiology has been shown in ***Figure 1.***

Figure 1 : **Pathophysiology of SARS-CoV2**



Pathophysiology of COVID-19-CXCL-10, C-X-C motif chemokine ligand 10; IFN, interferon; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MIP-1 , macrophage inflammatory protein-1 ; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; TNF- , tumour necrosis factor- ; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor[1].

Monoclonal Antibodies in COVID-19

Current research is going on for the evaluation of role of monoclonal antibodies (MAB) against the cytokines involved in the pathophysiology of COVID-19 infection. This article focuses on current trials involving use of monoclonal antibodies in COVID-19.

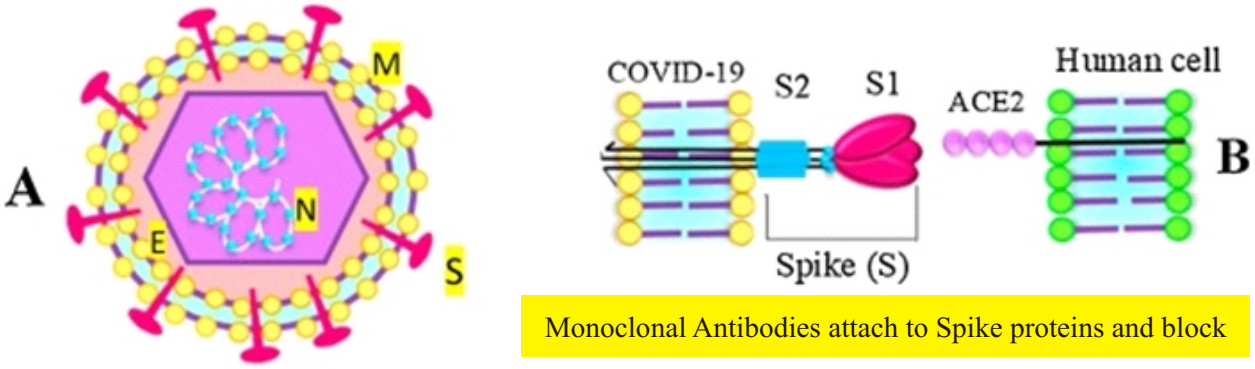
The main target of SARS-CoV-2 neutralizing monoclonal antibodies is the surface spike glycoprotein that mediates viral entry into host cells. Essentially all monoclonal antibodies of interest target this protein. Viral infection is mediated by the interaction between the viral spike protein and the angiotensin-converting enzyme 2 (ACE 2) receptor found on numerous cell types, but neutralizing monoclonal antibodies block this event[5]. Neutralizing antibodies have an important role in the protection or recovery from many viral infections. Several monoclonal antibody products will enter clinical trials over the next few months and be assessed for their ability to limit or modify SARS-CoV-2 infection. In addition, a drug that reliably prevented progression of COVID-19 would greatly reduce the concerns and uncertainty associated with SARS-CoV-2 infection and give physicians a therapeutic tool they must have for their patients. Establishing the therapeutic or prophylactic efficacy of monoclonal antibodies would be a major advance in the control of the COVID-19 pandemic[6].

Most monoclonal antibodies identify the S1 fragment of SARS-CoV and Receptor Binding Domain (RBD), and can block the interaction of RBD and its ACE2 receptor ***(Figure 2).*** Some monoclonal antibodies recognize the epitopes in unit S2 of SARS-CoV and suggest that other mechanisms may play a role in neutralization. The combination of monoclonal antibodies targeting S-proteins in SARS-CoV detects different epitopes in laboratory and in vivo cells that can be potentially effective at the viral level[7].

Tocilizumab

Tocilizumab is a humanized monoclonal antibody directed against the membrane and soluble forms of the IL-6 receptor. It was the first MAB used in COVID-19. Initially used to treat patients with Rheumatoid arthritis it was hypothesized to combat cytokine release syndrome in severely ill COVID-19 patients. Tocilizumab has been associated with an increased risk of infection, neutropenia, and thrombocytopenia; the hematologic abnormalities appear to be reversible upon stopping the drug. In addition, this agent has been shown to increase LDL cholesterol. However, it is not known yet if this

Figure 2 : **Site of action of Monoclonal Antibodies in COVID 19**



effect on lipid levels increases the risk for development of atherosclerotic disease[8].

Efficacy in COVID-19 :

Tocilizumab is one of the most widely used and widely studied MAB for COVID-19. Numerous clinical trials have been conducted and are under way, globally. Initially it was used as an off label treatment with little evidence. All studies being pandemic driven, were single Centre studies, with methodological flaws and design problems. Initial studies reported benefit with Tocilizumab. Early findings from the REMAP-CAP trial have suggested that tocilizumab significantly improves outcomes for critically ill patients with severe COVID-19, potentially reducing mortality and time spent in intensive care[9]. Patients who received tocilizumab were 44% less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care according to late-stage clinical data.

Tleyjeh IM et al in their Systemic review and Meta analysis included 24 studies (5 RCTs and 19 Cohorts) and concluded that cumulative moderate-certainty evidence shows that tocilizumab reduces the risk of mechanical ventilation in hospitalized COVID-19 patients. While RCTs showed that Tocilizumab did not reduce short-term mortality, low-certainty evidence from cohort studies suggests an association between Tocilizumab and lower mortality. They did not observe a higher risk of infections or adverse events[10]. The EMPACTA trial conducted in hospitalised patients with COVID-19 pneumonia who were not receiving mechanical ventilation, tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death, but it did not improve survival. Clinical failure as assessed in a time-to-event analysis favouredTocilizumab over placebo (hazard ratio, 0.55; 95% CI, 0.33 to 0.93). Death from any cause by day 28 occurred in 10.4% of the patients in the Tocilizumab group and 8.6% of those in the placebo group. In the safety population, serious adverse events occurred in 38 of 250 patients (15.2%) in the tocilizumab group and 25 of 127 patients (19.7%) in the placebo group. No new safety signals were identified[11].

Another major randomized control clinical trial-COVACTA, the phase III trial results were disappointing. The trial failed to meet its primary endpoint of improved clinical status. Tocilizumab did not improve patient mortality, although Tocilizumab-treated patients spent roughly a week less in hospital compared with those given placebo. There were many questions raised as COVACTA's eligibility criteria were broad and did not appear to stratify patients by clinical signs of hyperinflammation. Full trial data is still awaited including those on SARS-CoV-2 viral loads and inflammatory marker trends over the entire study period. An important point would be the time of drug administration, which is agreed upon by most researchers i.e at the onset of inflammatory response before development of respiratory failure[12].

In yet another RCT 243 patients with moderate disease were enrolled to compare the hazard ratio for intubation or death in the Tocilizumab group with the placebo. Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalised patients with COVID-19. Some benefit or harm could not be ruled out, however, because the confidence intervals for efficacy comparisons were wide[13]. In a preliminary RCT on patients with COVID-19 and pneumonia requiring oxygen support but not admitted to the intensive care unit, Tocilizumab did not reduce WHO-CPS scores lower than 5 at day 4, but might have reduced the risk of NIV, MV, or death by day 14. No difference on day 28 mortality was found[14].For hospitalised adult patients with COVID-19 pneumonia and partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio of between 200-300 mmHg, Tocilizumab had no benefit on disease progression compared with standard care[15].

Few noteworthy Ongoing trials for Tocilizumab include REMAP-CAP-which will evaluate Tocilizumab & other immunomodulators vs No immunomodulation, RECOVERY-Low dose Dexamethasone and Tocilizumab along with Convalescent plasma, now recruiting only children. TOC- COVID-19 is a Phase III clinical trial, part of a

global effort, to assess whether Tocilizumab might have therapeutic value for COVID-19 patients who have developed or at high risk of developing serious lung damage from SARS-CoV-2 infections

Safety Concerns : The major problems with Tocilizumab include Early infections leading to sepsis, and late infections. Adverse reactions are increase in serum cholesterol, AST, ALT, and injection site reaction. Threat of Reactivation of Tuberculosis is always there. Drug interactions are also common[16].

Itolizumab - In India this was the second most common MAB used in COVID-19 patients. Itolizumab is a first-in-class anti-CD6 monoclonal antibody that was initially developed for various cancers and was later developed and approved in India for treatment of moderate to severe chronic plaque psoriasis in 2013. This drug is now being re-purposed for COVID-19. The potential utility of itolizumab in COVID-19, based on its unique mechanism of action in ameliorating cytokine release syndrome (CRS), was proposed first in Cuba with approval of a single-arm clinical trial and expanded access use. Subsequently, a phase II, open-label, randomized, placebo-controlled trial has been conducted in 30 COVID-19 patients in India after receiving regulatory permission. Based on the results, the Indian drug regulatory agency recently approved itolizumab in July 2020 for 'restricted emergency use' for the treatment of CRS in moderate to severe acute respiratory distress syndrome (ARDS) due to COVID-19. The data and results have been analyzed skeptically and more evidence is needed to justify its use[17].

MAB in COVID-19 have laid the foundation for clinical trials involving different types of antibodies with different sites and modes of actions. The search for a potent and efficacious and safe MAB goes on…

Sarilumab - Sarilumab is a human monoclonal antibody that inhibits IL-6 mediated signalling through both the soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R).

Canakinumab - Canakinumab is a human monoclonal antibody of the IgG1 isotype. The antibody binds to human IL-1 and neutralizes its activity by blocking the interaction with IL-1 receptors, but it does not bind IL-1 or IL-1 receptor antagonist (IL-1Ra). This MAB was also tried in treatment of Acute Myocardial Infarction.

Anakinra - Anakinra is the recombinant form of the naturally occurring IL-1 receptor antagonist. Although anakinra has seen limited use for the treatment of RA, it has enjoyed a resurgence of late as an effective therapy of some rare inherited syndromes dependent on IL-1 production. Anakinra Inhibits IL-1, which is vital in the immune response to SAR-CoV-2. It might help to neutralise the cause of acute respiratory distress syndrome (ARDS) among patients with COVID-19[18].

Baricitinib - Baricitinib is Janus-associated tyrosine kinase (JAK) 1 and JAK 2 inhibitor, indicated for treatment of rheumatoid arthritis. It modulates the immune response by regulating overactive signalling through the Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway. May potentially combat cytokine release syndrome (CRS) in severely ill patients. Currently no known published controlled clinical trial evidence supporting efficacy or safety of Baricitinib alone in patients with COVID-19.

There is evidence that Baricitinib plus Remdesivir was superior to Remdesivir alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19, notably among those receiving high-flow oxygen or non-invasive ventilation. The combination was associated with fewer serious adverse events[19].

Some upcoming and investigational MABs and kinase inhibitors with relevant trials have been mentioned in ***Table 1 & Table 2.***

Table 1 : **List of Monoclonal Antibodies and trials underway**

Drug	Property	Ongoing Trials
Sarilumab	IL-6 receptor	• REMAP-CAP • Evaluation of the efficacy and safety of sarilumab in hospitalised patients with COVID-19.
Canakinumab	IL-1	Study of Efficacy and Safety of Canakinumab Treatment for CRS in Participants With COVID-19-induced Pneumonia (CAN-COVID)
Anakinra	IL- 1	REMAP-CAP
Ravulizumab	complement component 5 (C5) inhibitor	TACTIC-R
Gemtuzumab ozogamicin	CD33	CATALYST
Namilumab	GM-CSF inhibitor	CATALYST
Infliximab	TNF-	CATALYST
Adalimumab	TNF-	AVID-CC
Otilimab	GM-CSF	OSCAR
Risankizumab	IL-23	ACTIV-5 / Big Effect Trial (BET-A) for the Treatment of COVID-19
Lenzilumab	GM-CSF	ACTIV-5 / Big Effect Trial (BET-B) for the Treatment of COVID-19
Medi3506	Interleukin-33	ACCORD
Leronlimab	CCR5 receptor	Study to Evaluate the Efficacy and Safety of Leronlimab for Patients With Severe or Critical Coronavirus Disease 2019 (COVID-19)
LYCoV555/ bamlanivimab	the spike protein on SARS-CoV-2.	BLAZE-2, BLAZE-1, ACTIV-2, ACTIV-3
LY-CoV016/ Etesevimab	SARS-CoV-2 spike protein	BLAZE-1

Conclusion :

To conclude, Monoclonal antibodies can be used in COVID19 moderate and severe illness. The use must be selective and individualised. Recommended use should beearly as possible in moderate and severe COVID-19 before patients need noninvasive or invasiveventilatory support. Patients should not have leucopenia or leukocytosis. They should have normal values of liver enzymes and creatinine. They should have bilateral and progressive lung involvement. They should have significant elevations of inflammatory markers e.g. IL-6 > 40 or CRP> 10 mg/dl, Sr Ferritin, Sr LDH Sr D-Dimer and/or progressive increase in Fibrinogen levels. Remedesivir, Dexamethasone or Methylprednisosne, Enoxaparin can be used with

Table 2 : **Enzyme inhibitors and Ongoing trials in COVID-19**

Drug	Property	Ongoing Trials
Opaganib	sphingosine Kinase-2 (SK2)	Opaganib, a Sphingosine Kinase-2 (SK2) Inhibitor in COVID-19 Pneumonia
Razuprotafib	activates Tie2 receptor proteins	RESCUE
Baricitinib	tyrosine kinase (JAK) 1 and JAK 2	COV-BARRIER
Ruxolitinib	JAK 1 and JAK 2	• RUXCOVID • RUXCOVID-DEVENT
Acalabrutinib	Bruton's tyrosine kinase inhibitor	• ACCORD • CALAVI
Brensocatib	Reversible inhibitor of the dipeptidyl peptidase-1 enzyme	STOP-COVID19
Bemcentinib	AXL kinase	ACCORD-2

MAB but dose of warfarin will have to be adjusted. Physicians should exercise all possible caution while using monoclonal antibodies.

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