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Targeting "Cytokine Storm" for Therapeutic Benefit in COVID19 Patients

Dr. Dileepraja Yedla

MD General Medicine

Abstract: ***Cytokine storm plays important role in COVID mortality. So it is very essential to prevent and treat cytokine storm in COVID 19 patients.***

Keywords: Cytokine Storm, COVID-19

1. Introduction

The corona virus COVID 19 affecting 195 countries in the world. WHO called it as a global emergency. Until now total 3.8 lakhs patients affected with COVID 19. One lakh patient completely recovered and more than 16 thousand people died. Case fatality rate about 5%.now the active cases about2.5lakhs, among these 12 thousand patients are very sick they're treating in intensive care units.

Our country **India,** now in second phase of pandemic with total number of patients just crossing 500 with 10 deaths and case fatality rate about 2%. Due to the factors like huge population (138 cores), population density of 464/km^2, overcrowding and poverty there are high chances to enter into a third phase pandemic (community spread) very soon. If that happens it is disastrous compared to other developed countries like US, UK, FRANCE (now they are third phase) with total number of cases per million populations138, 98,304respectively.

Where's countries like *Italy& Switzerland* number of positive cases per million populations very high more than 1000 cases with high mortality and they failed to control COVID19 in spite of having advanced health care facilities.

To combat against COVID19 our main goals are two:

1) To break the chain i.e. community spread through preventive measures like social distancing, repeated hand wash etc.
2) To stop the disease progression from milder illness to life threatening severe acute respiratory depression with multi organ dysfunction requiring mechanical ventilator support.

WHO guidelines giving very much importance to ventilator support in managing sick cases. But countries like India, it is very difficult to provide ventilators and intensive care units once community outbreak occurs (third phase) with a large number of sick patients. So, always better to stop disease progression from mild to severe.

2. Pathophysiology of COVID 19:

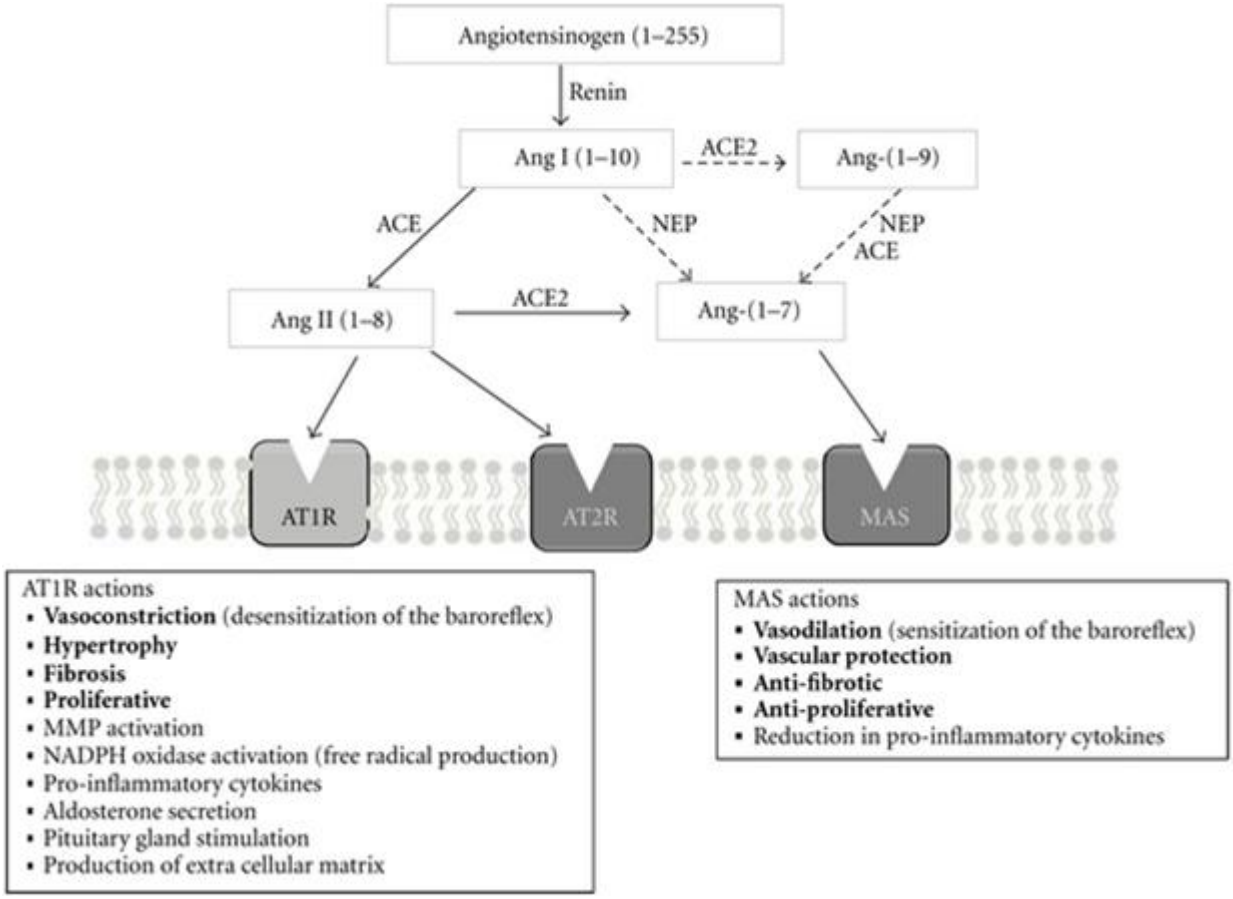
Virus attached to ACE 2 receptor Angiotensin converting enzyme 2 leads to dysregulation of rennin-angiotensin system. This plays a central role in the pathophysiology of COVID-19 associated acute lung injury (ALI)/acute respiratory distress syndrome (ARDS).

Angiotensin I is converted to angiotensin II by ACE. Angiotensin II mediates vasoconstrictive, pro-inflammatory and pro-oxidative effects through agonism at Angiotensin II receptor type 1 (AT1).

ACE2 converts AngiotensinII to angiotensin 1-7 (Ang1-7), which through binding Mas receptor (MasR) mediates anti-inflammatory, anti-oxidative and vasodilatory effects.

Hence, the ACE2/Ang1-7/MasR axis opposes the actions of the ACE/AngII/AT1 axis.COVID-19 appears more severe in patients with hypertension, cardiovascular disease and diabetes. These disorders are associated with decreased baseline levels of ACE2 expression.

We postulate here that SARS-CoV-2 binding to ACE2 may attenuate residual ACE2 activity, further skewing the ACE/ACE2 balance to a state of predominant ACE/AngII/AT1 axis signalling, in which Angiotensin 1 causes pulmonary vasoconstriction, and inflammatory and oxidative organ damage, ultimately progressing towards ALI/ARD[2]



Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines.

Significantly high blood levels of cytokines and chemokines were noted in patients with COVID-19 infection that included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA.

The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, anemia. Combined with the incidence of ground-glass opacities, and acute cardiac injury (some patients presenting like coronary artery disease).

Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα (cytokine release syndrome) that are reasoned to promote disease severity. Some patients develop secondary HLH.

Secondary Haemophagocytic Lymphohistiocytosis (SHLH) is an under-recognised, hyper inflammatory syndrome characterised by a fulminant and fatal hypercytokinaemia with multi-organ failure. In adults, SHLH is most commonly triggered by viral infections.

Cardinal features of SHLH include unremitting fever, cytopenias, and hyperferritinaemia; pulmonary involvement (including ARDS) occurs in approximately 50% of patients.

A cytokine profile resembling SHLH is associated with COVID-19 disease severity, characterised by increased interleukin (IL)-2, IL-7, granulocyte colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumournecrosis factor-α. Current management of COVID-19 is mainly supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) and cardiac injury are the leading causes of mortality.

3. Pathology of Cytokine Storm

Pro-inflammatory cytokines or chemokines can lead to the recruitment of inflammatory cells. Then, an increasing expression of inflammatory, antiviral, and apoptotic genes occurs accompanied by abundant immune cell infiltration and tissue damage.

However, for severe inflammation associated with cytokine storm, more serious pathological changes are observed, such as diffuse alveolar damage, hyaline membrane formation, fibrin exudates, and fibrotic healing. These are signs of severe capillary damage, immuno-pathologic injury, and persistent organ dysfunction.

Moreover, the severe inflammatory cytokines/chemokines can spill over into the circulation and result in systemic cytokine storms, which are responsible for multi-organ dysfunction

The inflammatory response begins when the pathogen-associated molecular pattern (PAMP) from the virus is recognized by the pattern recognition receptors (PRRs) of

innate immune cells, then, specific pro-inflammatory cytokines are expressed after the downstream signalling cascades off PRRs are triggered by stimuli. Researchers have a great interest in exploring the association between polymorphisms of PRRs and host susceptibility to cytokine storm, which may help explain why some individuals, but not others, seem relatively resistant to cytokine storm.

Severe cytokine storm, with markedly higher levels of pro-inflammatory cytokines including Interferons (IFNs), Tumor necrosis factors (TNFs), interleukins (ILs), and chemokines, has been detected in patients hospitalized with severe influenza infections. Severe cytokine storm is rarely observed in seasonal and other mild influenza, indicating that high cytokine/chemokine levels correlate strongly with disease severity. The interferon family has a critical role in the innate immune response to viruses.

A number of proteins with antiviral or immunomodulatory properties are produced once the IFN signalling pathway is activated. Although overproduction of IFN in the early stage of infection likely leads to irreversible lung damage, the IFN signalling pathway may also be important in restricting the dissemination of virus. TNF-α is a key cytokine in cytokine storm and is likely to account for the escalation in severity. However, TNF receptor$^{-/-}$ mice, or mice treated with anti-TNF-antibodies, have no changes in survival when compared with controls following a challenge with the H5N1 virus. IL-1 and IL-6 are the main pro-inflammatory cytokines released by hosts during viral infections. IL-1 is expressed in the early stages of infection, followed by an increasing expression of IL-6. [3]

Cytokine storm is the major immunological phenomenon causing life threatening disease manifestations like respiratory failure, acute kidney injury, Cardiac injury hepatopathy, thrombo cytopenia, hemodynamic compromise and leading cause of mortality.

So, Antioxidants, ulinastatin, low dose steroids, intravenousimmunoglobulin's monoclonal antibodies play significant role in prevention and treatment of cytokine storm and its effects.

This strategy has been used in the treatment of viral-induced cytokine storm and was confirmed to have improved the outcome in infections, such as SARS and the 2009 H1N1 pandemic influenza

Although the precise molecular events surrounding cytokine storm have not been clarified, immunemodulatory strategies and novel approaches in targeting the host's response to severe disease have been advocated.

Considering that these agents work on different intracellular pathways, they might ideally be used in combination to obtain a better outcome.[3]

Diagnostic Confirmation of Cytokine Storm:

All patients with severe COVID-19should be screened for hyper inflammation using laboratory trends (e.g., increasing levels of proinflammatory cytokines & ferritin, decreasing platelet counts, erythrocyte sedimentation rate) and cytokine levels along with routine lab investigation i.e. Hemogram, Liver & Renal Function Tests, CRP, PT, APTT, Complete Urine Examination, ECG, Chest Radiograph & Ultrasound Abdomen.

Treatment Options:

While the outbreak of COVID-19 was intensifying and spreading globally, 382 trials were registered between 23 January and 8 March (379 registered in China) on the WHO's International Clinical Trials Registry Platform (ICTRP), some of which might affect morbidity and mortality and help us understand the disease.

Now no directly acting antiviral agent against **COVID19**available.Ritonavir in combine with lopinavirnow using in severe cases but the effects are not promising. **Now the world busy in developing newer regimens, vaccines to fight against COVID19**.Trials showed Antimalarial Hydroxy chloroquine has some beneficial effects in both in prophylaxis and treatment. But it effects in very sick patients yet to be established. It has contraindicated certain groups of populations.

So, while waiting for research results and randomized control trail evidences for new antiviral agents we can target against immune dysregulation and proinflammatory cytokines.

Current immunomodulatory strategies for the treatment of cytokine storms in severe viral infections, including corticosteroids, peroxisome proliferator-activated receptor agonists, sphingosine-1-phosphate receptor 1 agonists, cyclooxygenase-2 inhibitors, antioxidants, anti-tumor-necrosis factor therapy, intravenous immunoglobulin therapy, interleukin-6antagonist (i.e. Tocilizumab) andother potential therapeutic strategies.[4]

Antioxidants:

Several randomized clinical studies in humans that have found that n-acetylcysteine (NAC) has role in treating cytokine storm because reactive oxygen species (ROS) play a central role in inflammatory responses. N-acetylcysteine (NAC), a modified form of the amino acid cysteine, was shown to inhibit the viral replication ,pro-inflammatory molecules (e.g., IL6, CCL5, CXCL8, and CXCL10) in lung epithelial cells, However, current evidence indicates that monotherapy using antioxidants had a limited effect on cytokine storm, and a combination of antiviral would still be needed.[5,6,7]

Intravenous Immunoglobulin:

Therapy uses concentrated globulin(IVIG) preparations from pooled human plasma for the treatment of acute infections. The mechanism by which IVIG suppresses harmful inflammation has not been definitively identified. It is believed to involve multiple immunomodulatory effects by blocking Fc receptors, which are associated with tolerance to self and severity of the inflammatory state.[8,9]

Tocilizumab:

Recently **US Food and Drug Administration** (FDA) has formally approved its phase 3 trial of tocilizumab in severely ill COVID-19 patients, who have been hospitalised with

pneumonia. Actemra (tocilizumab) – an interleukin-6 inhibitor – has already been approved in China for the treatment of patients infected with the **novel corona virus disease**, who have developed serious lung damage and also have elevated levels of IL-6 in the blood.

Previous research has suggested that elevated IL-6 – a biomarker for inflammation and a high-level immune response – is associated with a higher mortality in people with community-acquired pneumonia.

The investigation of Actemra's use in COVID-19 is based on the hope that the drug could interrupt the process of 'cytokine release syndrome' (CRS), a form of serious inflammatory response that can occur as a complication of some infections.[10,11,12]

Ulinastatin
Urinary Trypsin Inhibitor (also called ulinastatin or UTI) is an important protease inhibitor found in human urine, blood, and other tissues. It has been shown that UTI plays an anti-inflammatory role by decreasing the phosphorylation of p38 mitogen-activated protein kinase and nuclear factor-κbactivationas well as an antiapoptotic role by protecting the mitochondria and scavenging oxygen free radicals, and it can decrease the level of inflammatory mediators and reduce the frequency of immune cell apoptosis in sepsis models.

Therefore, UTI has been proposed as a potentially new therapeutic option for the treatment of sepsis and multiple organ dysfunction syndrome (MODS).13,14.

4. Conclusion

Mechanical ventilator support alone may not be sufficient to decrease mortality in patients with **severe ARDS and Carditis.** So, we have to target main pathological basis of the disease i.e. Cytokine Storm, to improve survival of these patients.

So, in moderate form of disease along with hydroxyl chloroquine addition of N acetyl cysteine definitely improves outcome, prevents disease progression and hastens the recovery without incidence of major side effects.

In critically ill patients' addition of ulinastatin along with the above drugs and in very sick patients with ventilator support. If they are affordable, we can trytocilizumab or ankinra but there's a risk of major side effects.

Mild to moderate case –Antipyretics, Antitussives, Hydroxyl Chloroquine**400mg BD** for **01 day** followed by **200mg BD** for **05 days** along with other supportive medicines.

Consider following Treatment Options:

- Inj. N acetyl cysteine 100mg/ kg bodyweight intravenously in divided doses daily for 05 days.
- Inj. vitamin C 1.5 mg intravenous OD for 05 days as a supportive treatment for to prevent Cytokine Storm & Disease progression.

Severe case:
Along with above medications**, Inj. Ulinastatin 1million IU intravenously once daily for 7 days.**

In very severe patients on ventilator support –
Along with above medications high dose **Intravenous Immunoglobulins25gm / day for 3 days.**
-Or-

Tocilizumab (as per recent trials in China) an Initial dose of 4–8 mg/kg infused over more than 60 minutes. If initial dose not effective, may administer second dose (in same dosage as initial dose) after **12 Hours**. No more than **2 Doses** should be given; maximum single dose is **800 mg.**

Compared to other immunomodulators and monoclonal antibodies.

N acetylcysteine, Ulinastatin, Tocilizumab are very much effective with no major side effects we can give to large number of patients as a treatment along with the antiviral drugs and other supportive measures. (Mild, moderate, severe COVID 19 grading as per WHO guidelines).

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