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Outcome of COVID-19 patients treated with and without monoclonal antibody – adalimumab, along with conventional antiviral therapy

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***Abstract*---**Background- The current outbreak of viral pneumonia, caused by novel coronavirus SARS-CoV-2, is the focus of worldwide attention.Based on their mechanism of action and their demonstrated utility in chronic inflammatory conditions and early feasibility studies in COVID-19, there is a strong case for TNF inhibitor use in COVID-19. Objectives-To find out the Outcome of covid 19 patients treated with and without monoclonal antibody – Adalimumab, along with conventional antiviral therapy. Methods-A Retrospective case comparative study of 100 patients with COVID19 who were admitted in VMKVMCH COVID19 Ward, Salem from May 2021 to July 2021 was included in this study. Purposive sampling technique was used.

Demographic details of the patients and outcomes were noted.SPSS (Version 22.0) was used. Results- Males were mostly affected (65%) as compared to females (35%), mean age was 49 years. Number of days in hospital stay was 8 days. Mortality was around 4%.RTPCR was the investigation of choice for the diagnosis of COVID done in 93% of patients and it was statistically significant ($p<0.05$), but due to severity of symptoms HRCT was the gold standard investigation. 97% has CORADS score greater than 5 and it was significant. Injections of monoclonal antibodies was given in 50% of patients, while antiviral (favipiravir) was given in 96% of patients which was comparable as they were not significant ($p>0.05$). As seen the mortality was only 4% this suggests outcomes of COVID with or without adalimumab was not significant. Among 4% died almost all the patients had taken monoclonal antibody. Conclusion- Adalimumab may be a valuable therapeutic agent for the management of patients with COVID-19 pneumonia considering its rapid clinical responses but it was not significant in terms of outcomes.

***Keywords*---**COVID-19, Adalimumab, favipiravir, RTPCR, viral pneumonia, dexamethasone,

Introduction

The current outbreak of viral pneumonia, caused by novel coronavirus SARS-CoV-2, is the focus of worldwide attention. The WHO declared the COVID-19 outbreak a pandemic event on Mar 12, 2020, and the number of confirmed cases is still on the rise worldwide.[1] While most infected individuals only experience mild symptoms or may even be asymptomatic, some patients rapidly progress to severe acute respiratory failure.[2] Recently, increasing studies indicate that the "cytokine storm" may contribute to the mortality of COVID-19[3]. The International Classification of Diseases (ICD) does not include the cytokine storm or CSS. Cron and Behrens bring the current knowledge of CSS[4]. They define that “cytokine storm” is an activation cascade of auto-amplifying cytokine production due to unregulated host immune response to different triggers. The triggers involved infections, malignancy, rheumatic disorders, etc. Another scholar described that cytokine storm is a systemic inflammatory response to infections and drugs and leads to excessive activation of immune cells and the generation of pro-inflammatory cytokines[5]. One review shows that SARS-Cov-2 selectively induces a high level of IL-6 and results in the exhaustion of lymphocytes.Several studies analyzing cytokine profiles from COVID-19 patients suggested that the cytokine storm correlated directly with lung injury, multi-organ failure, and unfavorable prognosis of severe COVID-19[6,7]

Cytokine Storm

A severe immune reaction in which the body releases too many cytokines into the blood too quickly. Cytokines play an important role in normal immune responses, but having a large amount of them released in the body all at once can be harmful. A cytokine storm can occur as a result of an infection, autoimmune

condition, or other disease. It may also occur after treatment with some types of immunotherapy. Signs and symptoms include high fever, inflammation (redness and swelling), and severe fatigue and nausea. Sometimes, a cytokine storm may be severe or life threatening and lead to multiple organ failure. Also called hypercytokinemia.Once a cytokine storm occurs, it can quickly cause single organ or multiple organ failure, and eventually becomes life-threatening.[6]

The need for effective therapies to reduce disease mortality and COVID-19 related damage in patients is increasingly evident, despite the development of vaccination strategies. Based on their mechanism of action and their demonstrated utility in chronic inflammatory conditions and early feasibility studies in COVID-19, there is a strong case for TNF inhibitor use in COVID-19[6] To overcome this cytokine storm many strategies have been used. Each covid centers follows their on institutional policy. Patient with moderate to severe covid 19 pneumonitis can develop cytokine storm at any point. To overcome this cytokine storm many strategies have been used. Besides corticosteroids, Adalimumab a recombinant TNF alpha IgG1 monoclonal antibody, blocks the inflammatory activity of TNF alpha , and specifically binds to TNF alpha and blocks its interaction with p55 and p75 cell surface TNF receptors and also lyses surface TNF – expressing cells in vitro and modulates biologic responses responsible for leukocyte migration.[7,8] In our study we have used the anti TNF Alpha - ADALIMUMAB along with conventional antiviral therapy.

Materials and Methods

A Retrospective case comparative study of 100 patients with COVID19 who were admitted in VMKVMCH COVID19 Ward, Salem from May 2021 to July 2021 was included in this study. Purposive sampling technique was used.

Inclusion criteria

1) Patients who were admitted with RT-PCR positive or CT thorax - CORADS 4 and above (CORADS - COVID-19 Reporting and Data System) with CT severity > 40%
2) Age > 18 years
3) Having raised CRP, D-dimer, and serum ferritin results within 24 hours after admission.
4) Saturation less than 90%
5) Respiratory rate higher than 24 per minute
6) Clinical signs of Cytokine storm.

Exclusion criteria

1) Age less than 18 years
2) Patients diagnosed with Sepsis
3) CT severity less than 40%
4) Allergy to adalimumab.
5) Pregnant and lactating patients
6) Known HIV positive or active Hepatitis B or C
7) Patients with Malignancy

8) Hematological disorders like severe thrombocytopenia, anaemia.
9) Previously treated with any other monoclonal antibodies before treatment with adalimumab.

Methodology

All patients who were admitted in covid-19 ward fulfilling the inclusion criteria were included in this Retrospective Case Comparative study. Those patients who have given consent for the use of inj. Adalimumab were considered as study group and those who were not given consent for use of inj. Adalimumab were considered as control group. Study group was given inj. Adalimumab 40mg sc 12 hours apart 2 doses were given. Both control and trial group were treated with antiviral medications, Low molecular weight heparin, steroids and other supportive care according to the institutional covid-19 treatment protocol. Patients' blood samples were collected on every third day till discharge and CT thorax were taken on every third day and evaluated. Patient's vitals and clinical parameters are recorded daily, outcome and recoveries were noted. Number of days of hospital stay, oxygen requirement, NIV requirement, mortality and morbidity was assessed.

Statistical Analysis

Analysis of data was done by using SPSS software ver. 22. Data were statistically described in terms of mean (±SD), frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Student t test for independent samples if normally distributed. For comparing categorical data, Chi square test was performed. A probability value (p value) less than 0.05 was considered statistically significant.

Results

Table 1- Demographic details of study Patients (N=100)

Variable		Number (%)
Age (years)		49±21
Gender	Male	65 (65)
	Female	35 (35)
Average no. of days in hospital		8 (8)
Mortality (outcome)		4 (4)

As per table 1 it was seen males were mostly affected (65%) as compared to females (35%), mean age was 49 years. Number of days in hospital stay was 8 days. Mortality was around 4%.

Table 2- Hemodynamic parameters among study patients

Parameters		Number (%)
Pulse rate	Normal	67 (67)
Tachycardia		33 (33)

Respiratory rate	Normal	90 (90)
	Tachypnea	10 (10)
Blood pressure	Normal	72 (72)
Hypertension		28 (28)
Oxygen saturation	>90%	90 (90)
<90		10 (10)

As per table 2 the hemodynamic parameters among COVID patients were seen. 33% of patients had tachycardia, 10% had higher respiratory rate than normal. 28% had hypertension and only around 10% has oxygen saturation less than 90.

Table 3- Investigation for the diagnosis of COVID

Investigation		Number (%)	p-value
RTPCR	YES	93 (93)	0.01
	NO	07 (7)	
HRCT	CORADS (1-4)	03 (3)	0.01
	CORADS ≥5	97 (97)	
Severity score	Mild	7 (7)	0.01
	Moderate	12 (12)	
	Severe	81 (81)	

As per table 3 as seen RTPCR was the investigation of choice for the diagnosis of COVID done in 93% of patients and it was statistically significant ($p<0.05$), but due to severity of symptoms HRCT was the gold standard investigation. 97% has CORADS score greater than 5 and it was significant.

Table 4- Management of COVID-19 in study patients

Management		Number (%)	p-value
Inj. AdalimumabYES		50 (50)	0.11
NO		50 (50)	
Favipiravir	YES	96 (96)	0.17
	NO	04 (04)	
Inj.LMWH0.4	YES	99 (99)	0.21
NO		01 (1)	

As per table 4 injections of monoclonal antibodies was given in 50% of patients, while antiviral (favipiravir) was given in 96% of patients which was comparable as they were not significant ($p>0.05$). As seen the mortality was only 4% this suggests outcomes of COVID with or without adalimumab was not significant. Among 4% died almost all the patients had taken monoclonal antibody. Injection LMWH was given in almost 100% of patients, similarly antibiotic (augmentin) given in 93% of patients. Along with steroids like dexamethasone was nearly given in most of the patients but that was not significant. Nebulization with Budecort and duolin was done in all patients.

Discussion

In the present study we have used the anti TNF Alpha - ADALIMUMAB along with conventional antiviral therapy for the management of COVID patients. Patients with severe acute respiratory syndrome (SARS) were reported to have elevated levels of cytokines in blood and cytokine gene expression in peripheral blood mononuclear cells (PBMC) with most of the patients were males and mean age of 44 seen in most of studies.[4,5,6] The mechanism of SARS-CoV infection inducing the release of cytokines remains obscure. Since the S protein can bind to the receptor, we sought to investigate whether the S protein can interact with macrophages then up-regulate the release of cytokines/chemokines.[5]

It has been demonstrated by Huang c and Ruan q that viral infection triggered the NF-κB pathway, resulting in transcription activation of a large number of proinflammatory genes, including cytokine and chemokines. To delineate the mechanisms of S protein inducing cytokine production, we first measured NF-κB activation by luciferase assay in S protein-induced RAW264.7 increased 5-fold compare to the control which increases the changes of respiratory infection with deranged hemodynamic parameters.[7,8] In our study, 33% had tachycardia and tachypnea in 10%. As per Patel S activation of NF-κB depends on degradation of I-κB, which normally sequesters NF-κB in the cytoplasm, inhibiting its function shows 44% patients had tachycardia.[6] Although immune cells lack ACE2, SARS-CoV can infect human macrophages and dendritic cells, without producing infectious virus particles, suggesting that SARS-CoV can entry the immune cells via other receptors. Toll-like receptors (TLRs), a major class of molecular pattern recognition receptors, are activated by direct interaction of the extracellular domain of the receptor with a pathogen-associated molecular pattern, resulting in activation of NF-κB, IRF3, and MAPK signaling pathways. TLR family is responsible for activation of innate immunity in response to various pathogens, including certain viruses which is the mechanism of high laboratory parameters like CRP, Interleukin and Ferritin in our study and high CORADS and severity score.[9,10,11]

IL-6, a pleiotropic factor, is a downstream target protein of NF-κB, on the other hand, IL-6 can also influence NF-κB activation. Neutrophils were incubated with IL-6 for 30 min, I-κB degradation was observed [11]. Outcomes with Monoclonal antibody in our study was not significant. ($p>0.05$) our results are in accordance with other studies [6,10,11,12]. We have a hypothesis that SARS-CoV interact with macrophages through the interaction between spike protein and the TLR on the cell surface, leading to activate multiple intracellular pathways involved inflammation, including activation of NF-κB and production of IL-6 and TNF-α in our study. IL-6 could activate NF-κB and up-regulate TLR expression via autocrine/paracrine effects, then aggravate the inflammation.[12]

Conclusion

Adalimumab is a recombinant fully human IgG1 monoclonal antibody that binds to TNF-α and inhibits its interaction with the p55 and p75 cell surface TNF receptors. According to the current knowledge of the authors and the mentioned evidence, adalimumab may be a valuable therapeutic agent for the management

of patients with COVID-19 pneumonia considering its rapid clinical responses but it was not significant in terms of outcomes in the present study when compared with antiviral medications.

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Conflict of Interest- None declared

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