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Original Research Article

A retrospective study of the role of Tocilizumab in preventing or controlling cytokine storm in COVID-19 cases

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ABSTRACT

Introduction: In spite of the advancement in science we are still lacking definite specific treatment for Covid-19. And till date (11^{th} April 2022) 6,203,372 and 5,21,722 death occurred globally and in India respectively. The sudden increase of O2 demand with need for Invasive ventilator is an indicator/ is a warning for cytokine storm Syndrome (CSS) or an over action of the immune system, which can be disastrous. Steroids are still the best anti-inflammatory drugs available thus as soon as a patient shows signs of a 'cytokine storm,' steroids should be used. Other drugs i.e. IL-6 receptor blocker TCZ and Sarilumab and direct IL-6 inhibitor Siltuximab [1] and JAK inhibitors (baricitinib) etc are also been considered in various trials for cytokine storm.

Materials and Methods: A retrospective observational study was performed in hospitalized patients referred from the district hospital to the Dedicated Covid Hospital (DCH), all were diagnosed with COVID-19 with hypoxemia.

Conclusion: The timely detection of CSS & early initiation to controlling management is the key issue The early identification of cytokine strom with initiation of TCZ may give beneficial result. The Oxygen requirement and CRP showed a significant decline with the use of tocilizumab. Furthermore, the optimal timing, dosage and administration route of TCZ may need to be studied with larger sample or with multicenteric study plan.

1. Introduction

Medical science can still recall the deadly Spanish Influenza pandemic outbreak (also referred to as Bombay Influenza/ Bombay Fever in India), almost a century back in 1918-1920. This lead to near 75 million deaths globally while India lost more than 15 million that is 5% of the then population. The comparison of 1918 influenza and COVID-19 pandemics has had similarities in the socio-economic implications [2] also. In spite of the advancement in science we are still lacking definite specific treatment for Covid-19. And till date (11^{th} April 2022) 6,203,372 and 5,21,722 death occurred globally and in India respectively.

Covid-19 pandemic virus is most notorious in respect of rapid mutation, and so far many variant been identified with different virulence. The clinical manifestations of COVID-19 vary widely among the 1^{st}, 2^{nd} and 3^{rd} wave. The 2^{nd} wave was most devastating with mortality and morbidity involving younger age groups, from mild to severe cases with pneumonia, acute respiratory distress syndrome (ARDS), and some with multi organ dysfunction. These cases often required invasive mechanical ventilation (IMV) but still mortality remained the high. [3]

In several studies, the markedly elevated inflammatory markers (e.g. CRP, D-dimer, ferritin etc) and elevated pro-inflammatory cytokines (including interleukin IL-6, IL-1,

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TNF-α) were associated with critical and fatal COVID-19, and while blocking these inflammatory pathway could prevent disease progression, [1,4]

The sudden increase of O2 demand with need for Invasive ventilator is an indicator/ is a warning for cytokine storm Syndrome (CSS) or an over action of the immune system, which can be disastrous. Steroids are still the best anti-inflammatory drugs available thus as soon as a patient shows signs of a 'cytokine storm,' steroids should be used.

Apart from symptomatic management & O2 therapy, the therapeutic options were limited for Covid-19. Neutralizing the virus through passive immunity i.e. monoclonal Antibodies/ Plasma therapy, or inhibiting viral replication (remdesivir), or dealing with the immune response to prevent untoward manifestations such as CSS, acute respiratory distress syndrome, and multisystem organ failure (glucocorticoids, interleukin- 6 antagonists, etc) are some options were tried. In patients with Covid-19, interleukin-6 levels are correlated with viral load, disease severity, and prognosis. [5] More specific available drug for IL-6 antagonist is Tocilizumab (TCZ). So we have under taken TCZ in this study to better understand the precise use of drugs that have been used to prevent CSS and disease progression along with steroids. Other drugs i.e. IL-6 receptor blocker TCZ and Sarilumab and direct IL-6 inhibitor Siltuximab [1] and JAK inhibitors (baricitinib) etc are also been considered in various trials.

2. Objective

To predict the cytokine storm clinically or with the help of biomarkers and to assess the efficacy of tocilizumab in preventing or controlling cytokine storm induced morbidity and mortality.

3. Materials and Methods

A retrospective observational study was performed in hospitalized patients referred from the district hospital to the Dedicated Covid Hospital (DCH), all were diagnosed with COVID-19 with hypoxemia. Clinical examination for disease severity was assessed and all were admitted to Respiratory Intensive Care Unit (RICU) of R.D. Gardi Medical College. The laboratory investigations including inflammatory Markers i.e. CRP, Ferritin, LDH, NL Ratio, D-dimer etc were performed on the day of admission. All the severe cases with clinical suspicion of CSS who were deteriorating on O_2, corticosteroid and supporting management were given TCZ as an adjuvant therapy. [4] TheInjection TCZ 400 mg was given as a single dose slow intravenously (over 1 h) after dilution in 100 ml of normal saline. A change in hypoxemia/ SpO2/ vitals/ and biological marker with any untoward or adverse drug reaction was recorded. This study is being done to evaluate the clinical response to drug TCZ.

4. Observations and Result

All the observation and results are presented in a tabular form with gross inference for further interpretation and evaluation.

5. Discussion

The higher rate of infectiousness with development of symptoms specially shortness of breath and the declining Oxygen Saturation rendered hospitalization to be very essential. The rapid increase in mortality has attracted the attention worldwide with detection of a new virus and declaration of Covid-19 pandemic on August 2020. The raised inflammatory biomarker with radiological (Chest X-Ray/ CT Thorax) evidence and declined SpO2 (< 90) helped in stratifying disease severity without any dispute. The present study included 40 severe case of Respiratory Intensive Care Unit (RICU), all had been referred from district hospital with advanced disease. The median age was 56.4 years and most (82.5 %) were males but no significant association observed between gender and age with the severity of lung involvement. [6] All had bilateral pneumonia predominantly in the lower and peripheral zones. The biomarkers may be helpful in assessing prognosis i.e. CSS as well the mortality rate. All the cases were already on steroids while injection TCZ was given and this study was to retrospectively evaluate for improvement in O2 requirement and decline of biomarker values. Preeti Malik et al analyzed 32 studies with 10491cases of confirmed COVID-19 and found that laboratory biomarkers including elevated CRP, Ferritin, D-dimer, LDH, PCT, CK, AST, ALT, creatinine and lymphopenia, thrombocytopenia were significantly associated with poor outcomes in COVID-19 patients. [7]

CRP is a sensitive biomarker of inflammation, infection, and tissue damage. Studies showed that it increased significantly in severe Covid – 19 patients at the initial stage, and further rose in severe form of interstitial pneumonia, and often evolved into acute respiratory distress syndrome (ARDS) which is a signal of lung damage and disease progression. [7] Hodges G, et al (cohort of 1310 patients) [8] mentioned that elevated CRP was independently associated with death/ICU admission after adjusting for age, gender, diabetes, hypertension, ischemic, heart disease or COPD. In our study we observed significantly raised CRP in all the cases and this correlates well with severity and showed reduction in levels in almost all (97.5 %) cases following treatment, however the mortality rate was 25 % among the total cases under trial for tocilizumab.

Besides CRP other inflammatory markers also need to be examined. An initial raised LDH (95%) and Ferritin (52.5) were found in this study. More death among raised LDH during hospitalization was observed while no definite conclusion could be made for ferritin. The ferritin is a

Table 1:

No.	Parameters	Results	Inference
1	Total cases	40	a) Survived (N=30) 75% b) Died (N=10) 25%
2	Male	33 (82.5 %)	Male predominant
3	M : F ratio	2.3	
4	Mean Age	56.4 Years	
5	Bilateral Pneumonia	40 (100%)	
6	Hypoxaemia (O_2 supported)	40 (100%)	Critical (N=31) 77.5 %
	1. Mechanical Ventilator. . . .22.5 %	Critical 77.5 %	
	2. BiPAP support. . . . . .40.0 %		Needed additional supported O2 therapy, among them survived 21 (68%).
	3. High flow O_2 support. . . ..15.0 %	22.5 %	
	4. * NRBM, Mask & Nasal prong. 22.5 %		
7	1. Co morbidity Present 28 cases (70%)	Death among	
	2. None morbid (N=12). . . . .30.0 %	None 30%	Morbid/non morbid Proportion of death equal in both group (25%). In co morbid group more death among two or with > two ailments group.
	Single morbidity . . . . . .30.0 %	Single 20%	
	3. Double morbidity. . . . . .27.5 %	Double 40%	
	4. > two co morbidity . . . .12.5 %	>two 10%	
7.1	Type of Co morbidity N=28 (70%)	Death	More than double the death among co morbid patients while cardiovascular diseases predominated.
	Diabetes . . . . . (55 %)	DM 60%	
	Systemic hypertension . . . ..(44 %)	HT 30%	
	Coronary Artery Disease (15%)	CV 40%	
8.	Inflammatory Biomarkers		
8.1	CRP: Initially: Raised in all Cases. . . 100 %	CRP declined after treatment with TCZ in (97.4%) cases. In spite 25% death observed	All the cases found with Initial raised CRP. All most all cases including those who died responded to TCZ treatment with decreased of CRP.
	Declined with TCZ Treatment . . . 97.4%		
8.2	Ferritin:		
	Normal. 52.5%	19.4% (4) Died	
	Initial Raised. . . . . 47.5 %	15.8% (3) died	
	Repeat Test in (9 cases) after treatment of them:		Could not find any relation to Morbidity & mortality
	Normal to Increased (3)	0 (Death)	
	Improved (4)	1 Died (25%)	
	Further Increased (2)	2 Died (100%)	
8.3	LDH: Raised values (38 cases). . . . . 95% *	20 % Died 50 % Died	More death among patients with raised in LDH during hospitalization.
	After treatment Values declined 37.5% *		
	Further increased values or . . . . .27.5% no change observed		
8.4	D-dimer	Death %	Initial Raised D-dimer was found in 72.5 % of cases with death of only 20 % while Initial Normal value with consecutive sudden increased of D-dimer during hospital stay the death was 40 %
	Normal value. . . . . 10 %	25%	
	Normal initially then raised during Stay 15%	40 %	
	Initially Raised. 72.5%	20 %	
9	CBC: TLC raised in 50 % cases		
	a) Survived group. 36.6%		
	b) Died group . . . . . .80 %	Further rise of 40% & 63% in survival & died groups.	Death among increasing in TLC is higher Majority have lymphopenia and were more vulnerable to die
	Lymphopenia in 73 % cases (29)		
	a)Survived group . . . . . 70 %		
	b)Died group. 80%		
10	N/L Ratio: raised in (18) cases. . . . 45 %		
	a) Survival group. . . . . .10 cases	33%	Higher N/L ratio have more untoward output
	b) Died group .. . .8 cases	80%	
11	Platelets: Count	Death	Maximum Patients had normal platelet count & outcome were slightly better in normal count group 77% vs. 72%
	<1.5 Lac (Low). . . . . 35 %	28 %	
	>1.5 Lac (Normal). . . . . 65 %	23 %	

key mediator of immune disregulation that contributes to cytokine storm and it has been implicated in fatal outcomes by Covid – 19 when accompanied by CSS. Thereby those with elevated ferritin have high probability to experience serious complications.[6] D-dimer is another marker. Initial Raised D-dimer was found in 72.5% of cases with death of only 20 % among them, while initial normal value with consecutive sudden increased of D-dimer during hospital stay, the death was 40 % in our study. Micro embolism, refractory hypoxemia and disseminated intravascular coagulation (DIC) also had contributory factors in mortality among Covid-19.[6,7] A low initial platelets count (<150000) reported from 17 studies with sample size of 3481 cases of covid-19 showed significantly greater number of poor outcomes.[6,7] In this reference we observed that maximum patients had normal (65%) platelet count & outcome were slightly better in normal count group 77% vs. 72%, thus the platelet count (<150000) or thrombocytopenia had significant impact on poor outcomes

The other simple routine marker is lymphopenia, or Neutrophil vs. Lymphocyte ratio (NL Ratio). Lymphopenia had nearly threefold higher risk of poor outcomes.[7] In our study we also observed significantly raised NL ratio in 45 % of cases with 33 % in survival vs. 80 % in deceased group respectively showed more than twofold higher risk with lymphopenia. The association with inflammatory markers and acute phase reactivation likely reflects the CSS associated with severe infection and sequelae of severe sepsis and end-organ damage.[9,10] Nevertheless, bacterial super infection is an important consideration and a factor in COVID-19; for example, the study by Wang et al,[9] has reported 81.7% of patients who died with COVID-19 had an associated bacterial infection.[9–11] Our study also showed a further rises in repeat total leukocyte count in 40 % and 63% percent cases with survivals and deceased group of patients and are more likely to have super infection. However, it is also essential to identify that during acute phase there are non-specific markers of inflammation i.e. procalcitonin secretion is primarily a sensitive marker of bacterial infections.[10] It may help in distinguishing but somehow we have not done this test in all cases.

Associated co morbidity also remained an important contributory factor in the outcome of Covid-19. Most of the studies showed higher vulnerability for those with cardiovascular diseases and Diabetics and we too have observed that 28 cases (70%) had co morbidity while no increase in percentage of death was found. The co morbid patients (70%) in the present study found to have more than doubled the chances to suffer from covid-19 but no difference was found in the proportion of death with co morbid and non co morbid group, while those who had two or more than two simultaneous co morbidity are more vulnerable (>50%) to death. The advance age may be a contributory factor as well. Only 1 case (10% among died) had multi organ dysfunctions.

TCZ is a humanized monoclonal antibody IgG1 anti-human receptor for IL-6, it is therapeutically been applied in rheumatoid arthritis (RA) and systemic juvenile arthritis but it can be prescribed for COVID-19 patients with severe lung damage and high IL-6. TCZ has shown good efficacy in several clinical trials so far,[12] although mechanism of this drug in respiratory inflammation with COVID-19 is unclear.[13] The main pathophysiology of covid-19 itself is still unrecognized but increased worsening of inflammation can well be identified clinically with development of pneumonia, O2 demand and biological marker,[4,6–8,14] and this has been labeled as cytokine release syndrome (CRS) or Cytokine Storm syndrome (CSS)/ Inflammatory cytokine storm.[12,13,15] The timely detection of CSS and earlier initiation of controlling management is the key issue.[16,17] The steroid were invariably been given to all our patients prior to further intervention i.e. O2 management or add on TCZ therapy. We had used injection methylprednisolone 40 mg twice a day for a short course of 7-10 days. The Horby P. et al warned that high doses or wrong administration timing can be harmful as glucocorticoid delays viral clearance.[18]

The Danfei Liu et al mentioned that 58% patients showed a rapid improvement of clinical and respiratory condition and after ten days of TCZ treatment 80 % improved with return of laboratory results to the normal range, while mortality stood at 20%.[12] In our study we also observed rapid improvement in most of the cases with mortality of 25%, (one patient developed sepsis and later died) as against a survey of 137,000 adults, reported (by Jha et al.) 26 to 29% mortality.[19] The most important observation in this study was that Oxygen requirement and CRP regression were observed in all the cases.

In our study a single dose of TZN (400 mg) was used and no side effect were observed. In other studies adverse reaction were observed when higher doses and repeat therapy was followed and found to be in the range around 10%. Some of the studies have reported limited or no significant role of TCZ in respect to clinical improvement or survival in covid-19.[20–22] The use of TCZ in covid-19 is further need to be explore regarding when to initiate i.e. timing and doses schedule. (16, 18&26) The best result may be obtained to initiate TCZ with early detection of CSS but required further confirmation.

6. Conclusion

The timely detection of CSS & early initiation to controlling management is the key issue. The worsening infection of Covid-19 is clinically well recognized by development of bilateral pneumonia with supplementary demand of oxygenation, which further deterioration with increase in laboratory biomarkers. The early identification of cytokine strom with initiation of TCZ may give beneficial result. The

Oxygen requirement and CRP showed a significant decline with the use of tocilizumab. The Ventilation management may itself be a strategy to reduce the overall mortality. Furthermore, the optimal timing, dosage and administration route of TCZ may need to be studied with larger sample or with multicenteric study plan.

7. Source of Funding

None.

8. Conflict of Interest

None.

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