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To determine the effectiveness of Tofacitinib on treatment outcome in patients hospitalised with COVID-19 pneumonia- A longitudinal observational study in a tertiary care Hospital Mandya

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ABSTRACT

Introduction: The effectiveness of Tofacitinib, a Janus kinase inhibitor, in patients who are hospitalised with coronavirus disease 2019 (COVID-19) pneumonia are unclear hence this study is conducted to evaluate the efficacy of Tofacitinib on treatment outcome in patients hospitalised with COVID-19 pneumonia.

Materials and Methods: All diagnosed cases of SARS COV2 who required O2 therapy at the start of the study will be undergoing routine investigations according to COVID 19 management guidelines and will be treated with adequate immunosuppression with corticosteroids. Those patients whose inflammatory markers (CRP, S LDH, D DIMER) are not decreasing after 48 hours of corticosteroids therapy may be given Tab Tofacitinib 10mg bid for a period of 14 days or till the decrease in inflammatory markers, whichever is earlier. Oxygen requirement and inflammatory markers were assessed every 3^{rd} day.

Results: Out of 27 patients who didn't respond for corticosteroids 20 were given the drug tab tofacitinb 10mg BD. CRP in the both the steroid non responders and steroid responders groups was high till day 9, on day 14 the CRP levels were normal in 50% of steroid non responders. S LDH levels in the steroid non responders group was in the decreasing trend i.e., on day 14 it was normal in 70% of patients.. The levels of D DIMER in tofacitinib group was high till day 6, and on day 14 the D-DIMER levels were normal in 40% patients. Oxygen requirement showed drastic changes in the steroid non responders group.

Conclusions: Among patients hospitalized with COVID-19 pneumonia, addition of Tofacitinib to steroid non responders group showed early improvement in their clinical and biochemical levels. Hence, Tab tofacitinib can be recommended an adjunct to steroids for early clinical and biochemical improvement for treatment of moderate to severe cases of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a viral disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS -COV-2). Severe manifestations of sars-cov- 2 infection are associated with an exaggerated immune response driven by interleukin -6, tumor necrosis factor alpha, and other cytokines in a pattern called cytokine storm. [1]

1.1. Pathophysiology of COVID-19

Spike protein 'S' on virus envelope has Receptor binding domain (RDP) which binds to the ACE-2 receptor (angiotensin converting enzyme -2) present on the type 2 pneumocytes of the alveoli. ACE-2 is an enzyme which

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helps in converting angiotensin -2 to angiotensin.[1–7] Once the virus binds to the receptor it enters the cell through receptor mediated endocytosis and later undergo the process of viral replication and in turn cause injury to the host cell. This led to immune cells reach up to the host cell and help in apoptosis. As the type 2 pneumocytes decreases, the surfactant levels decrease, leads to ARDS.

Also, the ACE2 receptor gets shed of from the host cell and this leads to increased levels of angiotensin-2 (AG2). Increased AG2 will bind to AT1 R (angiotensin type 1 receptor) and AT1-R recruits and phosphorylates JAK2 and, based on the target cell, one of the STAT is phosphorylated by activated JAK2. This leads to hypertension, chronic tissue injury, activation of the immune system. Activated immune system leads to infiltration of immune cells and again these immune cells release cytokines with the help of JAK STAT.[8–15]

Simultaneously viral proteins, mRNA will be processed by the antigen presenting cells (APC'S) and presents the antigen to the CD 4 TH cells with the help of MHC 2. These CD4 T cells transform to memory cells and releases cytokines (IL2, IL6, TNF alpha) with the help of JAK-STAT pathway. Also, with the help of MHC1 the cytotoxic cells CD8 gets activated and releases cytokines and destroys the virus and also the host cells.

The four Janus kinase (JAK) receptors JAK1, JAK2, JAK3, Tyk-2, present on the surface of immune cells, will phosphorylase and activate signal transducers and activation of transcription (STATs), which in turn will modulate gene expression responsible for the production of numerous cytokines as interleukin (IL)-2, IL-4, IL-6, IL-7, IL-9, IL-10, IL-11, IL-15, IL-21 and IL-22. JAK 1 & 3, Tyk-2 are found ubiquitous and JAK-2 act in the hemopoietic lineage and exerts critical role in lymphocytic function.[2]

Tofacitinib is an orally administered selective inhibitor of Janus kinase (JAK) 1 and JAK3, with functional selectivity for JAK2, that blocks intracellular transduction pathways after a cytokine is bound to its receptor. As a con-sequence, no cellular response is triggered, and cytokine production is indirectly suppressed. Tofacitinib also modulates the action of interferons and interleukin-6, decreasing the release of cytokines by type 1 and type 17 helper T cells, which are implicated in the pathogenesis of the acute respiratory distress syndrome. Thus, the action of tofacitinib on multiple critical pathways of the inflammatory cascade may ameliorate progressive, inflammation-driven lung injury in hospitalized patients with COVID-19. It is an oral agent first approved by the FDA for the treatment of rheumatoid arthritis and has been shown to decrease levels of IL-6 in patients with this disease. Tofacitinib is also FDA approved for the treatment of psoriatic arthritis, juvenile idiopathic arthritis, and ulcerative colitis.

2. Materials and Methods

2.1. Study design

All diagnosed cases of SARS COV2 who required O2 therapy at the start of the study will be undergoing routine investigations according to COVID 19 management guidelines and will be treated with adequate immunosuppression with corticosteroids. Information is collected through structured proforma from each patient. A detailed systemic examination will be done. A detailed enquiry will be made about name, age, sex, address, symptoms and patients with history of immunosuppressive, current cancer therapy and breastfeeding and pregnancy status will be excluded from the study. Also, patients whose inflammatory markers are decreasing with steroids will be excluded from the study. Those patients whose inflammatory markers (CRP, S LDH, D DIMER) are not decreasing after 48 hours of corticosteroids therapy may be given Tab Tofacitinib 10mg bid for a period of 14 days or till the decrease in inflammatory markers, whichever is earlier, as per the discretion of the treating Physician. Routine investigations which include CRP, LDH, D DIMER is repeated every 3rd day according to the COVID-19 management guidelines and also the oxygen requirement in litres is documented and will be observed for the effectiveness of the drug.

2.2. Participants

41 patients were screened according the study design and 14 corticosteroid responders were excluded from the study. Out of 27 patients who didn't respond for corticosteroids 20 were given the drug tab tofacitinb 10mg bid. The clinical improvement in the form of oxygen requirement were assessed and biochemical inflammatory markers were assessed every 3^{rd} day.

Age distribution: Out of 20 patients in the tofacitinib plus dexamethasone group 7 patients were above 60 years of age, 6 patients were between 51-60 years of age, 4 patients were 41-50 years and 3 patients were below 40 years of age. In the dexamethasone only group, 3 patients were above 60 years and 3 were in between 51-60 years of age, 1 patient below 40 years.(Figure 1 and Table 1)

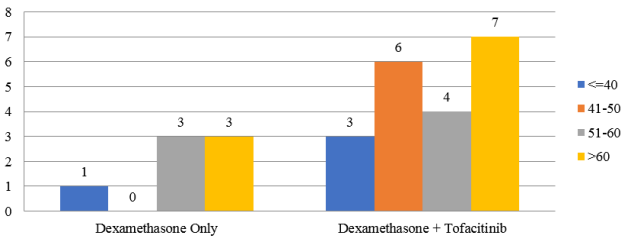

Figure 1: Age distribution

Table 1: Age distribution

Age (Years)	Dexamethasone Only	Dexamethasone + Tofacitinib	Total	P-value
<=40	1 (14.29%)	3 (15%)	4 (14.81%)	
41-50	0 (0%)	6 (30%)	6 (22.22%)	
51-60	3 (42.86%)	4 (20%)	7 (25.93%)	0.358
> 60	3 (42.86%)	7 (35%)	10 (37.04%)	
Total	7	20	27	

Sex distribution: 12 out of 20 patients were male and 8 patients were female in tofacitinib plus dexamethasone group. 3 male patients and 4 female patients in dexamethasone only group.(Figure 2)

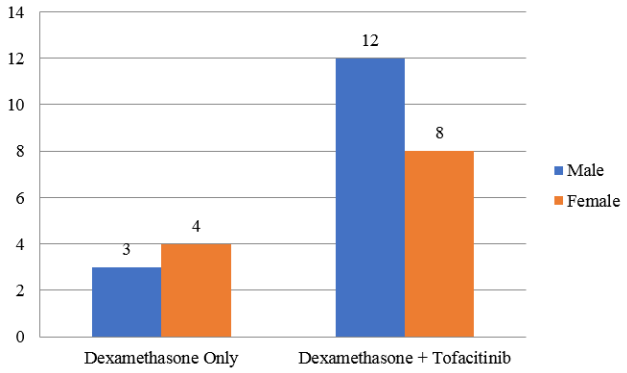

Figure 2: Sex distribution

3. Results

Mean CRP in steroid non responders' group (dexamethasone plus tofacitinib) were compared with dexamethasone only group. The standard deviation in both groups were high in both groups till day 9 of study, however in the tofacitinib group standard deviation from mean on day 14 were 0.95 and at p value at 5% level of significance compared with 2.51 in dexamethasone only group.(Table 2 and Figure 3)

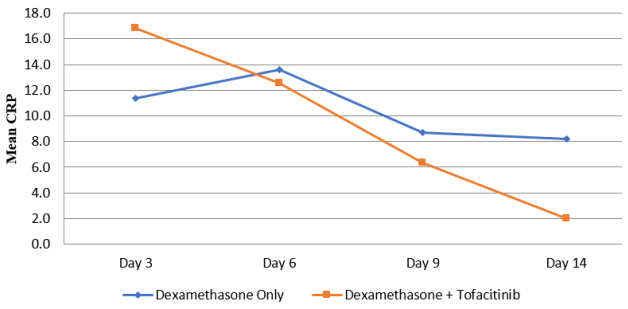

Figure 3: Mean CRP by visit

Mean S LDH values in steroid non responders and steroid responders groups were compared, the tofacitinib group had standard deviation of 117.7 from mean in day 9 which decreased to 41.58 on day 14 with p value significant at 5% level of significance compared with standard deviation of 135.45 & 113.68 on day 9 and day 14 respectively in dexamethasone only group which shows that addition of tofacitinib to the treatment had significant improvement in S LDH.(Table 3 andFigure 4)

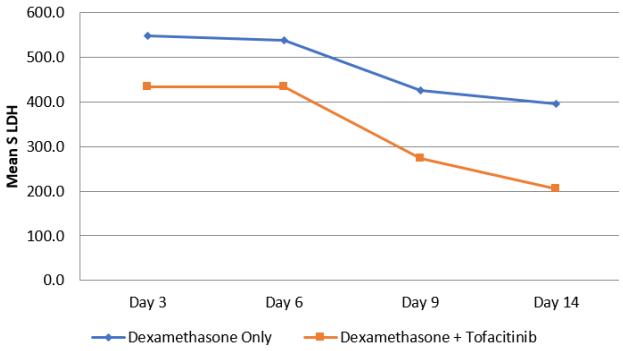

Figure 4: Mean S LDH by visit

Mean D DIMER values in steroid non responders and steroid responders groups were compared, the tofacitinib group had standard deviation of 0.66 from mean in day 9 which decreased to 0.65 on day 14 with p value significant at 5% level of significance compared with standard deviation of 1.50 & 1.05 on day 9 and day 14 respectively in dexamethasone only group which shows that addition of tofacitinib to the treatment had significant improvement in D DIMER.(Figure 5)

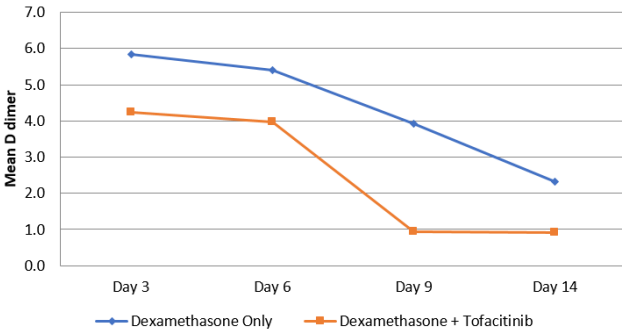

Figure 5: Mean D dimer by visit

Table 2: Mean comparison of CRP by treatment by visit

	Dexamethasone Only			Dexamethasone + Tofacitinib			P-Value
	N	Mean	Std. Deviation	N	Mean	Std. Deviation	
CRP at Day 3	7	11.36	7.18	20	16.81	9.53	0.181
CRP at Day 6	7	13.61	6.16	20	12.54	6.80	0.715
CRP at Day 9	7	8.69	3.14	20	6.36	4.68	0.236
CRP at Day 14	7	8.23	2.51	20	1.97	0.95	<0.001*

P-value is based on two independent sample t-test.
* P-value is significant at 5% level of significance.

Table 3: Mean comparison of S LDH by treatment by visit

	Dexamethasone Only			Dexamethasone + Tofacitinib			P-Value
	N	Mean	Std. Deviation	N	Mean	Std. Deviation	
S LDH at Day 3	7	548.71	184.10	20	434.15	105.53	0.160
S LDH at Day 6	7	538.57	150.96	20	432.95	108.27	0.056
S LDH at Day 9	7	426.57	135.45	20	274.25	117.77	0.009*
S LDH at Day 14	7	396.14	113.68	20	205.70	41.58	0.004*

P-value is based on two independent sample t-test.
* P-value is significant at 5% level of significance.

Mean of oxygen requirement were studied amongst the steroid non responders and steroid responders groups, mean oxygen requirement in litres were 8.05, 8.30, 6.30, & 1.15 on day 3, day 6, day 9, day 14 respectively amongst the tofacitinib plus dexamethasone group which showed significant decrease in the mean oxygen requirement with significant p value at 5% level of significance at day 9 and day 14. However, the mean oxygen requirement was 9.43, 11.57, 12.14, & 11.83 on day 3, day 6, day 9, day 14 respectively in the dexamethasone only group and showed no improvement in the oxygen requirement, also one patient succumbed in the dexamethasone only group.

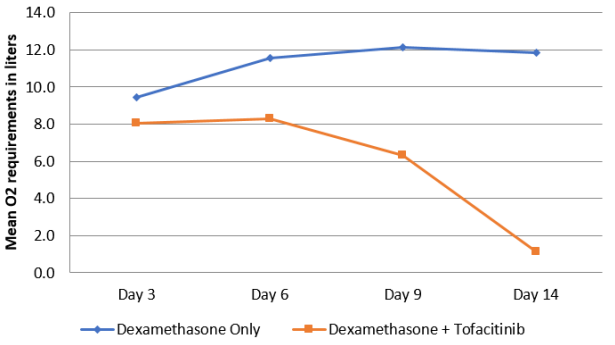

Figure 6: Mean O2 requirements in liters by visit

4. Discussion

In a randomised, double blind, placebo-controlled trial by Patricia O. Guimaraes et al, a total of 289 patients underwent randomization at 15 sites in Brazil. Overall, 89.3% of the patients received glucocorticoids during hospitalization. The cumulative incidence of death or respiratory failure through day 28 was 18.1% in the tofacitinib group and 29.0% in the placebo group. Death from any cause through day 28 occurred in 2.8% of the patients in the tofacitinib group and in 5.5% of those in the placebo group. The proportional odd of having a worse score on the eight-level ordinal scale with tofacitinib, as compared with placebo, was 0.60 at day 14 and 0.54 at day 28. Serious adverse events occurred in 20 patients (14.1%) in the tofacitinib group and in 17 (12.0%) in the placebo group. And the study concluded that, among patients hospitalized with Covid-19 pneumonia, tofacitinib led to a lower risk of death or respiratory failure through day 28 than placebo.

In this study we have compared the serum inflammatory markers and clinically the oxygen requirement in both the groups, i.e., dexamethasone plus tofacitinib (steroid non responders and dexamethasone only group (steroid responders). CRP (normal range 0 – 0.5 mg/ dl) in the both the groups was high till day 9, on day 14 the CRP levels were normal in 50% of steroid non responders. S LDH levels in the tofacitinib group was in the decreasing trend i.e., the levels were high in all patient's day 3 and on day 9 it was high in 15(75%) patients and on day 14 it was normal in 70% of patients. However, in the dexamethasone only group the levels didn't decrease from day 3 to day 14 and was still on higher levels. The levels of D DIMER in tofacitinib group was high till day 6, later there was decrease in D dimer levels in 3 patients on day 9 and on day 14 the D-DIMER levels were normal in 8 patients. The levels of DDIMER did not decrease in the dexamethasone only group till day14.

Table 4: Mean comparison of O2 requirements in liters by treatment by visit

	Dexamethasone Only			Dexamethasone + Tofacitinib			P-Value
	N	Mean	Std. Deviation	N	Mean	Std. Deviation	
O2 requirements in liters at day 3	7	9.43	2.23	20	8.05	2.19	0.148
O2 requirements in liters at day 6	7	11.57	2.99	20	8.30	2.83	0.028*
O2 requirements in liters at day 9	7	12.14	2.79	20	6.30	2.62	<0.001*
O2 requirements in liters at Day 14	6**	11.83	2.93	20	1.15	3.72	<0.001*

P-value is based on Mann-Whitney U test.
* P-value is significant at 5% level of significance.**One patient died on Day 14.

Oxygen requirement showed drastic changes in the tofacitinib group, all the patients required oxygen on day 3 and oxygen requirement increased for all patients from the day of admission. Later on, day 6, 5 (25%) patients didn't require oxygen. 10 (50%) patients required the same amount of oxygen and 5 (25%) patients had increased requirement. However, on day 14, 18 (90%) patients didn't require oxygen supplementation and 1 (5%) patient required the same amount and 1 (5%) patient had increased requirement of oxygen. Comparing with the dexamethasone only group all the patients required oxygen supplementation with increase number of litres on day 3, on day 6, 5 (71.43%)patients had increased number of litres, 2 (28.57%) required same amount of oxygen. On day 9 oxygen requirement was increased in 5 (71.43%) patients and 2 (28.57%) required same amount, on day 14, 6 (85.71%) patients still required oxygen in same amount and didn't show clinical improvement and 1 (14.29%) patient succumbed to covid in this group.

5. Limitations

Sample size of 80 (40 patients in each group) was unable to reach due to less number of patients in COVID-19 3^{rd} wave and the statistical analysis was done for only 41 patients and results were given.

6. Conclusion

As 2 groups steroid non responders and steroid responders didn't have the equal number of patients for study, we couldn't conclude that patients in dexamethasone plus Tofacitinib group improved with addition of Tab tofacitinib and patients in dexamethasone only group didn't improve as tofacitinib wasn't started. However, the patients who were started with tofacitinib had improvement in clinical (oxygen requirement) and decrease in the elevated inflammatory markers compared with the patients who were not started on tofacitinib. The steroid non responders who were not started on tofacitinib didn't have decrease in the oxygen requirement and also didn't show much decrease in inflammatory markers. To conclude the patients started on tofacitinib showed early improvement in their clinical and biochemical levels. Hence, Tab tofacitinib can be recommended an adjunct to steroids for early clinical and biochemical improvement for treatment of moderate to severe cases of COVID-19.

7. Conflict of Interest

None.

8. Source of Funding

None.

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