Poster No. A0348

# TOFACITINIB AS AN ADJUNCT TO CORTICOSTEROIDS IN ACUTE SEVERE ULCERATIVE COLITIS: AN INTERIM ANALYSIS OF RANDOMISED PILOT STUDY

Manjeet Kumar Goyal, Arshdeep Singh, Shivam Kalra, Ramandeep Kaur, Dharmatama Singh, Yogesh Gupta, Ramit Mahajan, Vandana Midha, Varun Mehta, Ajit Sood

Dayanand Medical College & Hospital, Ludhiana, India

## Introduction

❖Ulcerative Colitis (UC) is a chronic inflammatory condition involving large intestine. 20-30% patients with UC have life time risk of developing Acute Severe Ulcerative Colitis (ASUC); defined as per Truelove and Witt's criteria and requires hospitalization with high mortality and short-term colectomy rate of 25-30%.

❖Intra-venous corticosteroids remain the first line therapy but still 30-40% patients don't respond to it and require salvage therapies such as cyclosporine, infliximab or colectomy.

❖Tofacitinib a pan Janus Kinase (JAK) inhibitor has been recently approved for moderately severe ulcerative colitis but its effect on steroid responsiveness in ASUC remains uninvestigated.

## Aims and Objectives

❖ To evaluate the effect of tofacitinib as an adjunct to intravenous hydrocortisone on steroid responsiveness in patients with ASUC.

## Methods

### Subjects

❖Adult patients (>18 years) with confirmed diagnosis of UC and hospitalized for ASUC (Truelove and Witts criteria) were enrolled after obtaining informed consent. Patients with Crohn's disease, clinical signs of fulminant colitis, toxic megacolon, or indeterminate, microscopic or infectious colitis, active or latent tuberculosis, malignancy (current or past), pregnancy or renal, hepatic, pulmonary, cardiac, neurological disease, etc. restricting the participation in the study were excluded.

### Randomization and Treatments

❖Patients were randomised in 1:1 ratio to receive either intra-venous (IV) hydrocortisone 100mg 6hourly with tofacitinib 10mg thrice daily or similar looking placebo as an adjunct for 7 days. The dose of tofacitinib was decreased to 10 mg twice daily from day 8 onwards and continued till week 8. IV hydrocortisone was shifted to oral prednisolone 40mg/day on day 8 and tapered by 5mg per week. Standard of care treatment was continued in both the groups.

### Outcomes

❖Primary outcome was steroid responsiveness (defined as<3 stools/day, or 3–8 stools/day with CRP <45 mg/L) after 72 hours of treatment.

❖Secondary outcome was colectomy free survival at week 8.

❖Subjects not satisfying Oxford criteria were offered infliximab/cyclosporine/colectomy as rescue therapy.

### Statistical Analysis

❖ Categorical variables were presented in the form of number and percentage (%). Quantitative variables with normal distribution were analyzed using independent t test while Mann Whitney test was used for data not that was not distributed normally. Qualitative variables were analyzed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used. p value <0.05 was considered statistically significant.

## Results

❖ 82 ASUC patients were enrolled in the study with 47 receiving corticosteroids plus tofacitinib whereas rest 35 received corticosteroids plus placebo. Baseline characteristics were similar in both the groups (table 1).

❖ Steroid responsiveness after 72 hours of treatment was found to be significantly higher in Tofacitinib + corticosteroids group (T) in comparison to corticosteroids alone group(S) (82.98% vs 57.14%; p 0.01) (table 2 and figure 1).

❖ However, there was no significant difference between the two groups in terms of colectomy free survival, CRP, fecal calprotectin and mortality rate between the 2 groups (table 3-6)

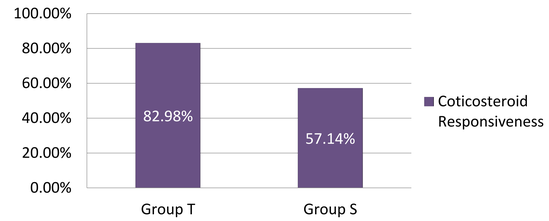
| Baseline Characteristics | Group T (n=47) | Group S (n=35) | p value |
|---|---|---|---|
| Age | 39.11±15.38 | 38±14.62 | 0.743‡ |
| Males | 24 (51.06%) | 22(62.86%) | 0.235† |
| CMV (IHC) | 9 (19.15%) | 3 (8.57%) | 0.22* |
| Clostridioides difficile | 2 (4.26%) | 5 (14.29%) | 0.131* |
| Albumin | 3.13 ± 0.84 | 2.86 ± 0.91 | 0.159‡ |
| CRP | 45.45 (13.48-69.065) | 41.52 (9.495-96.045) | 0.966§ |
| Fecal calprotectin | 2000 (2000-2000) | 2000 (2000-2000) | 0.124§ |

Table 1 Baseline characteristics between 2 groups § Mann Whitney test, ‡ Independent t test, † Chi square test, * Fisher's exact test

| Corticosteroid Responsiveness | Group T(n=47) | Group S(n=35) | Total | p value |
|---|---|---|---|---|
| No | 8 (17.02%) | 15 (42.86%) | 23 (28.05%) | 0.01† |
| Yes | 39 (82.98%) | 20 (57.14%) | 59 (71.95%) | |
| Total | 47 (100%) | 35 (100%) | 82 (100%) | |

Table 2 Comparison of steroid responsiveness after 72 hours of treatment between tofacitinib group (T) and corticosteroid group (S) † Chi square test

**Figure 1. Comparison of corticosteroid responsiveness between two groups**




| CRP (mg/L) | Day 0 | Week 8 | p value |
|---|---|---|---|
| Group T | 45.45 (13.48-69.065) | 2.4 (0.89-11.32) | <0.0001¶ |
| Group S | 41.52 (9.495-96.045) | 2.22 (0.982-10.34) | 0.005¶ |

Table 3 Comparison of CRP(mg/L) between group T and S. ¶ Wilcoxon Signed Rank Test

| Fecal Calprotectin (µg/g) | Day 0 | Week 8 | p value |
|---|---|---|---|
| Group T | 2000 (2000-2000) | 317 (97.75-1771.25) | <0.0001¶ |
| Group S | 2000 (2000-2000) | 176 (41.5-899.5) | 0.0002¶ |

Table 4 Comparison of Fecal calprotectin (µg/g) between group T and S. ¶ Wilcoxon Signed Rank Test

| Mortality | Group T(n=47) | Group S(n=35) | Total | p value |
|---|---|---|---|---|
| No | 44 (93.62%) | 30 (85.71%) | 74 (90.24%) | 0.277* |
| Yes | 3 (6.38%) | 5 (14.29%) | 8 (9.76%) | |
| Total | 47 (100%) | 35 (100%) | 82 (100%) | |

Table 5 Comparison of mortality between group T and S at week 8 of treatment.* Fischer exact test

| Colectomy free survival | Group T(n=47) | Group S(n=35) | Total | p value |
|---|---|---|---|---|
| No | 4 (8.51%) | 7 (20%) | 11 (13.41%) | 0.191* |
| Yes | 43 (91.49%) | 28 (80%) | 71 (86.59%) | |
| Total | 47 (100%) | 35 (100%) | 82 (100%) | |

Table 6 Comparison of colectomy free survival between group T and S at week 8 of treatment.* Fischer exact test

## Discussion

❖ In our study, steroid responsiveness was 82.98% in group receiving tofacitinib as an adjunct to corticosteroids in comparison to 57.14% with corticosteroids only group. The difference was found to be significant (p value <0.05).

❖UC is an inflammatory condition with high level of cytokines and cytokines exert their action via JAK-Signal Transducer and Activators of Transcription (JAK-STAT) pathway and tofacitinib being a JAK inhibitor may exert a synergistic action on corticosteroid action in UC.

❖Tofacitinib is currently being investigated as primary as well as rescue therapy in ASUC. In the current study, tofacitinib was used only as an adjunct to corticosteroids as the combination may be able to target two different pathways and may have a synergistic effect which may lead to a significant outcome and seems a scientifically plausible explanation.

❖This study forms a basis for conduct of a large randomized controlled trial to evaluate the role of tofacitinib as a measure to improve steroid responsiveness in ASUC.

## Conclusion

❖Tofacitinib as an adjunct to corticosteroids in the management of ASUC significantly enhanced corticosteroid responsiveness at 72 hours of treatment.

❖However, the difference between colectomy free survival and mortality rate was not statistically significant between 2 groups but numerical advantage was there. However, results need to be confirmed by larger randomized clinical trials.

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### Acknowledgements

We are very thankful to :
Dr. Gaurav, Dr. Mayur Luthra, Dr. Prabhjot Singh, Dr. Ashita Rukmini, Mr. Andrew Bhatti, Mr. Varinderjeet Singh, Mr. Pardeep Rawat, Ms. Simranjeet Kaur, Mr. Jatinder Negi



For more information:
Dr. Manjeet Kumar Goyal
Dayanand Medical College & Hospital, Ludhiana
Email: manjeetgoyal@gmail.com
+91-8285234620