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Efficacy And Safety Of Low Dose Tofacitinib As Induction Therapy In Moderate To Severe Ulcerative Colitis: A Pilot Study

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Abstract

Objective: The Inflammatory cascade has been the root cause of ulcerative colitis's pathogenesis, and its treatment would centre upon reducing its intensity. Tofacitinib, an orally administered micromolecule, blocks the Janus kinase (JAK) signal transducer pathway, thereby reducing mucosal inflammation. This observational study aimed to assess Tofacitinib's efficacy in relieving Ulcerative Collitis symptoms.

Methods: Out of 19 patients included in the study, only 09 completed the treatment as per inclusion criteria. The Patients were given 5mg of Tofacitinib daily for 6-8 weeks. Total Mayo score i.e. Stool frequency, Rectal bleeding, Endoscopic findings and physician global assessment and Partial Mayo score i.e. Total Mayo score minus Endoscopic findings were used as a parameter for disease severity characterization and Partial Mayo score was used as a parameter for measuring the response after treatment.

Results: Out of these patients, 05(50%) developed some sort of side effects prominently flatulence, abdominal discomfort, and generalized edema. Loss of coordination was observed in one 46-year-old male patient. The mean age of the patients presenting with UC was 43.4 years, with an average of 25.2 months of disease duration. The mean partial Mayo score improved from 5.40 to 2.90 after treatment with 5mg of Tofacitinib. The mean of the stool frequency improved significantly from 8.89 to 3.56.

Conclusion: Low-dose Tofacitinib is an effective option in the treatment of moderate to severe ulcerative colitis offering efficacy comparable to biologics with lesser side effects, no loss of efficacy over time and cost-effectiveness

Keywords: Ulcerative Colitis, Inflammation.

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1. Introduction

Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disease (IBD) of the colon that causes inflammation of the superficial mucosa to varying degrees from the rectum to the more proximal colon. Remissions and relapses characterize the course of UC.[1] Tenesmus, rectal urgency, and bloody diarrhoea are classic symptoms of UC.[2] Patients with UC often experience extra-intestinal manifestations (EIM), which can affect a wide variety of systems and share features with other autoimmune illnesses.[3-6] Ulcerative colitis (UC) is on the rise around the world.[7] In Asia, the incidence of inflammatory bowel disease is approximately between 0.5 to 3.4 per 100,000 people.[8] Algorithms for initiating, optimizing, and monitoring the efficacy of already available drugs have also undergone significant development. Annual direct and indirect costs for UC in the United States are expected to range from $8.1 to $14.9 billion respectively USA.[10,11] UC causes significant morbidity and decreased quality of life.[12] Active disease is associated with a higher risk of social isolation, career stagnation, and co-occurring psychiatric conditions such as anxiety and depression.[13] Persistent, uncontrolled inflammation is a significant risk factor in the development of dysplasia and colorectal cancer seen in patients with long-standing UC.[14] Therefore, the management of UC requires a prompt and accurate diagnosis, evaluation of the patient's risk of unfavourable outcomes, and initiation of effective, safe, and tolerable medical therapy.[15] The aims of treatment are maintenance of steroid-free remission for an extended period, provision of adequate psychosocial support, maintenance of a normal health-related quality of life, avoidance of morbid events such as hospitalization and surgery, and prevention of cancer. Understanding the best preventive, therapeutic, and diagnostic approaches is essential for achieving these objectives. The treat-to-target (T2T) method for inflammatory bowel disease (IBD) was described by the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) committee in 2015.[16,17] This method switched the focus of UC treatment to the long-term avoidance of illness consequences (hospitalizations,

colectomy, and dysplasia/cancer) and suggested monitoring of objective disease activity metrics. The T2T technique, which was developed from the paradigm for treating rheumatoid arthritis, tries to achieve disease remission by adjusting therapy in response to the fulfilment of preset therapeutic response targets (clinical remission, mucosal healing, effect on quality of life and wellbeing).

Tofacitinib is a synthetic medicine that suppresses JAK3, JAK1, JAK2, and TYK2 to a lesser extent.[18] The STRIDE committee grouped these two goals as a composite goal, but there was insufficient evidence to support the inclusion of histology and biomarker targets. It specifically and reversibly binds to the kinase's adenosine triphosphate (ATP) binding site. This activity inhibits signal transmission of type I and type II interferon receptors and several interleukins (IL-2, IL-4, IL-6, IL-7, IL-15, and IL-21), all of which play a role in the inflammatory and immunological response.[19] Therefore, it suppresses several cytokines relevant to the pathogenesis of UC as part of its mode of action

2. Materials & Methods

The current study was conducted at the Center for Liver and Digestive Disorders, Holy Family Hospital Rawalpindi, and The Advanced GI and Liver Clinic, Rawalpindi, Pakistan. Patients between the age of 18-64 years, with a confirmed diagnosis of Ulcerative Colitis (based on clinical, endoscopic and histological findings) were included. All had moderate to severe ulcerative colitis based on the Mayo score. These patients were previously untreated and have failed or are intolerant to corticosteroids or azathioprine. Tofacitinib in low doses (5mg twice daily) was used as an experimental drug for the treatment of UC. Exclusion criteria included a lymphocyte count below 750 cells/mm³, a neutrophil count below 1000 cells/mm³, and haemoglobin levels lower than 9 g/dL. Participants with any active infections, such as CMV, C. diff, tuberculosis, or HIV, as well as those with indeterminate colitis, microscopic colitis, ischemic colitis, infectious colitis, or findings suggestive of Crohn's disease, were also excluded. Additional exclusions applied to subjects with disease limited to the distal 15 cm, those showing clinical signs of fulminant colitis or toxic megacolon, and pregnant individuals. Prohibited concomitant therapies included TNF antagonists, azathioprine, methotrexate, and mercaptopurine.

10mg of tofacitinib in two divided doses per day was prescribed and induction of remission was observed in the 8th week from the start of the treatment. Total and partial Mayo scores, and stool frequency along with colonoscopic findings were used for the assessment of disease severity before starting treatment. SPSS 24.0 and Microsoft Excel 2019 were used for data analysis. Frequencies and percentages were calculated for qualitative variables such as gender, mucosal healing, clinical response, biochemical response, endoscopic remission, symptomatic remission, adverse effects, and improvement in quality of life. Means and standard deviations were calculated for quantitative variables, including age, total Mayo score, and partial Mayo scores.

Mayo Score: The Mayo score is an instrument designed to measure the disease activity of ulcerative colitis (UC). It consists of 4 sub-scores: *stool frequency*, rectal bleeding, *standardized colonoscopy findings* and *physician's global assessment* (PGA), each graded from 0 to 3. Higher scores indicate more severe disease. Scores are summed up to give a total score range of 0 to 12; where higher scores indicate more severe disease.

Partial Mayo Score: It utilizes 3 non-invasive components of the full Mayo score(stool frequency, rectal bleeding and physician's global assessment). It has a total score of 9 points. The following responses were monitored for assessment of induction of remission as well as drug efficacy and safety at 8th weeks.

- Onset of symptom improvement in days.
- Partial mayo score.
- Decrease in total stool frequency.
- Decrease in blood-containing stools frequency.
- Side effects.

3. Results

During the current clinical trials for the efficacy and prognostic effect of Tofacitinib, patients were also monitored for side effects 09 patients who were endoscopically and histopathological confirmed cases of Ulcerative colitis, were included in the study. Out of these patients, 05(56%) developed side effects prominently flatulence, abdominal discomfort, and generalized oedema. Loss of coordination was observed in one male of age 46 years. No other severe side effects were observed.

Table 1: Master data of patients on Tofacitinib treatment for UC

Age/sex	Tofacitinib duration	Symptom improvement onset in days	Total mayo score		Partial mayo score		Stool frequency		Frequency of bloody stools		Side effects
			pre-Rx	post-Rx	pre-Rx	post-Rx	pre-Rx	post-Rx	pre-Rx	post-Rx	
49/M	3 months	15 days	11		9	4	15x	3-4x	15x	0	Flatulence
38/M	9 months	2 weeks	11		9	4	15x	3-4x	8-10x	0	Flatulence
46/M	5 days	3 days	_	_	8	4	10x	7-8x	5-6x	0	generalized oedema, loss of coordination
46/F	1 month	1 week	9		7	4	10x	3-4x	10x	0	severe body aches
40/M	>1.5 months	2-3 days	6		5	3	2	1	2	1	Nil
34/F	2 months	1 week	4		3	2	2	1	0	0	Nil
32/M	1 month	1 week			5	3	4-5x	2-3x	4-5x	1	Nil
46/M	2 months	1 week	9		7	4	20x	6-7x	15x	1	Abdominal Pain, constipation
38/M	2.5 months	_	3		1	1	1-2x	1-2x	0	0	Nil

The mean age of the patients presenting with UC was 43.4±4.13 years, with an average of 25.2±4.70 months of disease duration.
The mean of the partial Mayo score improved from 6.4±1.3 to 3.6±0.96 (24.4-66.7% CI)
The mean stool frequency improved significantly from 15±2.49 to 4.6±1.04 (43.12-74.91% CI)
The mean frequency of blood-containing stools decreased from 9.2 to 0.2

Table 2: Disease Activity Parameters - Pre And Post Treatment

	Patient Mayo Score		Stool Frequency		Stools with blood Frequency	
Patient	Pre. Treat (n)	Post. Treat (n)	Pre. Treat (n)	Post. Treat (n)	Pre. Treat (n)	Post. Treat (n)
1	9	4	15	3-4	15	0
2	9	4	15	3-4	8-10	0
3	8	4	20	3-4	15	0
4	5	4	10	7	5-6	0
5	7	4	10	3-4	10	0
6	5	3	4-5	2-3	5-6	1
7	3	2	20	6-7	15	1
8	5	3	4-5	3-4	0	0
9	7	4	6-7	3-4	0	0

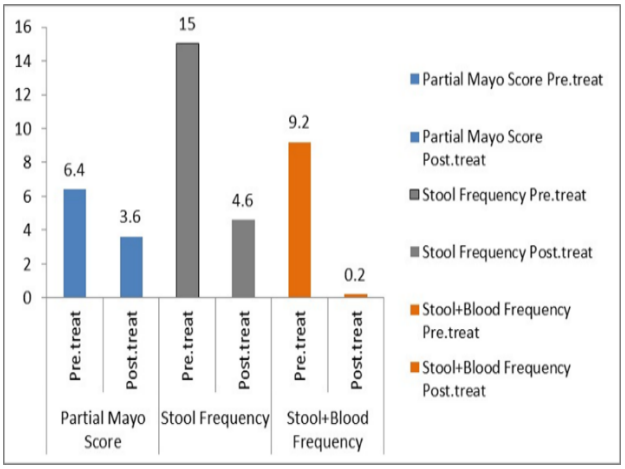

Figure 1: Disease Activity Parameters - Pre And Post Treatment

4. Discussion

The European Medicines Agency and the U.S. Food & Drug Administration have both approved tofacitinib for the treatment of moderate-to-severe UC based on the OCTAVE RCTs.[20] Tofacitinib has made great strides in the treatment of UC patients. Inhibiting the JAK/STAT cascade successfully prevents the chronic inflammatory cascade at multiple levels with few adverse consequences.[21] The main advantage is oral route of administration and no hospital visits as required for subcutaneous and intravenous preparations. The drug also withstands gastric breakdown. There is a rapid onset of action and excellent intestinal bioavailability with tofacitinib.[22] It has a shorter half-life as compared to

intravenous and subcutaneous formulations enabling its swift flushing out of the body if it needs discontinuation due to adverse events (AEs), before emergency surgery or if live vaccinations are to be administered.[23] Given that it is a tiny molecule rather than an antibody, it does not induce the production of antidrug antibodies causing loss of efficacy with time. One important disadvantage is lower compliance, which is the case with daily oral drugs like 5-ASA compounds, especially over long periods of treatment.[24] In several clinical trials, it was shown that the medication was effective in the achievement of clinical response and remission in patients who suffered from moderately severe to severe UC, both during the induction phase and during the maintenance phase of treatment. Tofacitinib's efficacy was demonstrated by the high rate of endoscopic and mucosal healing as well as a significant improvement in quality of life, which was demonstrated by a decrease in the patient's score on the IBDQ.[25-27]

Our study was the first of its kind in Pakistan that studied the efficacy of tofacitinib which too in a lower dose, induces remission in moderate to severe ulcerative colitis. Instead of the recommended 10mg dose, patients were given low 5 mg Tofacitinib daily to assess its efficacy in terms of clinical response. Most of the patients who presented had a mean disease duration of approximately 2 years but all the patients included in the study had not achieved symptom control with prior therapies or had become steroid-dependent for disease control. This led to poor quality of life, depression and decreased compliance to treatment as well. Moreover, they could not afford biologic agents like infliximab which is the oldest and highly efficacious biological agent used for induction and maintenance of remission of ulcerative colitis and has a pooled clinical remission rate of 85% according to a meta-analysis.[29] Our study results demonstrated a significant reduction in partial Mayo scores that includes non-invasive parameters of the full Mayo score (stool frequency, rectal bleeding and physician's global assessment). Of special note is the rectal bleeding sub-score that decreased to almost 0, defined as a response in previous studies conducted on other biological agents like infliximab.[28] It is observed that the results of our study were comparable to those conducted with biological agents. Also, no significant side effects that required medical attention were observed with low-dose tofacitinib.

Hence in the future tofacitinib has the potential to replace the biological agents in the treatment of UC patients owing to its easy route of administration, cost-effectiveness no loss of efficacy over time and lesser side effects.

Even with a very limited number of patients, the study results have clearly shown that the efficacy of tofacitinib especially in terms of rapidity of onset of symptom improvement, decrease in frequency of blood-containing stools as well as overall decrease in defecation frequency. It is a new drug and with a lower dose (5mg) no efficacy study has been done in Pakistan previously.

Medicine cost constraint was a major factor that led to a loss of follow-up by the patients and was a hindrance in achieving a better sample population during the current study. The inclusion of more patients in a fully funded study will have a better patient follow-up and can enhance a better understanding of the efficacy of the drug and related side effects. As the drug was tested and given to only a limited number of individuals, so current study may lack a better accuracy of results and dependency for future treatment recommendations of the drug.

5. Conclusion

Low-dose Tofacitinib is an effective option in the treatment of moderate to severe ulcerative colitis offering efficacy comparable to biologics with lesser side effects, no loss of efficacy over time and cost-effectiveness.

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References

1. Lang-Schwarz C, Agaimy A, Atreya R, Becker C, Danese S, Fléjou J-F, et al. Maximizing the diagnostic information from biopsies in chronic inflammatory bowel diseases: recommendations from the Erlangen International Consensus Conference on Inflammatory Bowel Diseases and presentation of the IBD-DCA score as a proposal for a new index for histologic activity assessment in ulcerative colitis and Crohn's disease. Virchows Archiv. 2021;478(3):581-94. https://link.springer.com/article/10.1007/s00428-020-02982-7
2. Gajendran M, Loganathan P, Jimenez G, Catinella AP, Ng N, Umapathy C, et al. A comprehensive review and update on ulcerative colitis. Disease-a-month. 2019;65(12):100851. https://doi.org/10.1016/j.disamonth.2019.02.004
3. Le C, Zeffren N, Kramer N, Rosenstein ED. Rheumatologic associations of microscopic colitis: A narrative review. Modern Rheumatology. 2022. https://doi.org/10.1093/mr/roac080
4. Rogler G, Singh A, Kavanaugh A, Rubin DT. Extraintestinal manifestations of inflammatory bowel disease: current concepts, treatment, and implications for disease management. Gastroenterology. 2021;161(4):1118-32. https://doi.org/10.1053/j.gastro.2021.07.042
5. Ribaldone DG, Pellicano R, Actis GC. The gut and the Inflammatory Bowel Diseases inside-out: The extra-intestinal manifestations. 2019. https://hdl.handle.net/2318/1706991
6. Buie MJ, BKin JQ, Windsor JW, Coward S, Hansen TM, King JA, et al. Global Hospitalization Trends for Crohn's Disease and Ulcerative Colitis in the 21st Century: A Systematic Review With Temporal Analyses. Clinical Gastroenterology and Hepatology. 2022. https://doi.org/10.1016/j.cgh.2022.06.030
7. Kumar R. Epidemiology of Life-Threatening Disease and Inflammation. Biomedical Journal of Scientific & Technical Research. 2021;39(2). https://doi.org/10.26717/BJSTR.2021.39.006268
8. Bhayani P, Natarajan K, Coelho-Prabhu N. Rising Incidence of Inflammatory Bowel Disease in the Asian Subcontinent—An Exploration of Causative Factors. Gastrointestinal Disorders. 2024 Jun 17;6(2):549-56 https://doi.org/10.3390/gidisord6020038
9. Du L, Ha C. Epidemiology and pathogenesis of ulcerative colitis. Gastroenterology Clinics. 2020;49(4):643-54. https://www.gastro.theclinics.com/article/S0889-8553(20)30073-X/abstract
10. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Gastroenterology Review/Przegląd Gastroenterologiczny. 2019;14(2):89-103. https://www.termedia.pl/Epidemiology-of-colorectal-cancer-incidence-mortality-survival-and-risk-factors,41,34580,0,1.html
11. Hood MM, Wilson R, Gorenz A, Jedel S, Raeisi S, Hobfoll S, et al. Sleep quality in ulcerative colitis: associations with inflammation, psychological distress, and quality of life. International journal of behavioral medicine. 2018;25(5):517-25.https://link.springer.com/article/10.1007/s12529-018-9745-9
12. Hnatyszyn A, Hryhorowicz S, Kaczmarek-Ryś M, Lis E, Słomski R, Scott RJ, et al. Colorectal carcinoma in the course of inflammatory bowel diseases. Hereditary cancer in clinical practice. 2019;17(1):1-9. https://link.springer.com/article/10.1186/s13053-019-0118-4
13. Agrawal M, Spencer EA, Colombel J-F, Ungaro RC. Approach to the management of recently diagnosed inflammatory bowel disease patients: a user's guide for adult and pediatric gastroenterologists. Gastroenterology. 2021;161(1):47-65. https://doi.org/10.1053/j.gastro.2021.04.063
14. D'Arcangelo G, Aloi M. Treat-to-target in pediatric inflammatory bowel disease: what does the evidence say? Pediatric Drugs. 2020;22(5):463-72. https://link.springer.com/article/10.1007/s40272-020-00406-2
15. Ungaro R, Colombel J-F, Lissoos T, Peyrin-Biroulet L. A treat-to-target update in ulcerative colitis: a systematic review. The American journal of gastroenterology. 2019;114(6):874. https://doi.org/10.14309/ajg.0000000000000183
16. Fernández-Clotet A, Castro-Poceiro J, Panés J. Tofacitinib for the treatment of ulcerative colitis. Expert Review of Clinical Immunology. 2018;14(11):881-92. https://doi.org/10.1080/1744666X.2018.1532291
17. Choy EH. Clinical significance of Janus Kinase inhibitor selectivity. Rheumatology. 2019;58(6):953-62. https://doi.org/10.1093/rheumatology/key339
18. Chimenti MS, Conigliaro P, Biancone L, Perricone R. Update on the therapeutic management of patients with either psoriatic arthritis or ulcerative colitis: focus on the JAK inhibitor tofacitinib. Therapeutic Advances in Musculoskeletal Disease. 2021;13. https://doi.org/10.1177/1759720X20977777
19. Hu X, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: From bench to clinic. Signal Transduction and Targeted Therapy. 2021;6(1):1-33. https://www.nature.com/articles/s41392-021-00791-1
20. Liu E, Aslam N, Nigam G, Limdi JK. Tofacitinib and newer JAK inhibitors in inflammatory bowel disease—where we are and where we are going. Drugs in Context. 2022;11. doi: 10.7573/dic.2021-11-4
21. Wong U, Cross R. Emerging drugs for the treatment of inflammatory bowel disease. Expert Opinion on Emerging Drugs. 2022.https://doi.org/10.1080/14728214.2022.2147507
22. Veloso PM, Machado R, Nobre C. Mesalazine and inflammatory bowel disease–From well-established therapies to progress beyond the state of the art. European Journal of Pharmaceutics and Biopharmaceutics. 2021;167:89-103.
23. D'amico F, Parigi TL, Fiorino G, Peyrin-Biroulet L, Danese S. Tofacitinib in the treatment of ulcerative colitis: efficacy and safety from clinical trials to real-world experience. Therapeutic Advances in Gastroenterology. 2019;12. https://doi.org/10.1177/1756284819848631
24. Sandborn WJ, Panés J, D'Haens GR, Sands BE, Su C, Moscariello M, et al. Safety of tofacitinib for treatment of ulcerative colitis, based on 4.4 years of data from global clinical trials. Clinical Gastroenterology and Hepatology. 2019;17(8):1541-50. https://doi.org/10.1016/j.cgh.2018.11.035
25. Taxonera C, Olivares D, Alba C. Real-world effectiveness and safety of tofacitinib in patients with ulcerative colitis: systematic review with meta-analysis. Inflammatory Bowel Diseases. 2022;28(1):32-40. https://doi.org/10.1093/ibd/izab011

26. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis. The New England journal of medicine. 2017;376(18):1723-36. https://doi.org/10.1056/NEJMoa1606910
27. Paul Rutgeerts, M.D., Ph.D., William J. Sandborn, M.D., Brian G. Feagan,et al. Infliximab for Induction and Maintenance
28. Therapy for Ulcerative Colitis. N Engl J Med 2005; 353:2462-2476. https://doi.org/10.1056/NEJMoa050516
29. Yang S, Yang S, Kwon Jo Y, Kim S, Jung Chang M, Choi J, Hee Cheon J, Yu YM. Efficacy and tolerability of infliximab retreatment in patients with inflammatory bowel disease: a systematic review and meta-analysis. Therapeutic Advances in Chronic Disease. 2021 Sep;12:20406223211041927. https://doi.org/10.1177/20406223211041927