

 ISSN NO. 2320-5407	Journal Homepage: -www.journalijar.com INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR) Article DOI:10.21474/IJAR01/12492 DOI URL: http://dx.doi.org/10.21474/IJAR01/12492	 INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR) ISSN 2320-5407 Journal Homepage: http://www.journalijar.com Article DOI:10.21474/IJAR01/12492
---	---	---

RESEARCH ARTICLE

COMPARISON AND EVALUATION OF TACROLIMUS VS STEROID THERAPY IN THE TREATMENT OF INFLAMMATORY BOWEL DISEASE IN ACTIVE PHASE

**Zeba Samreen¹, Minhaj Sultana¹, Mohd Shanawazuddin¹, Tahoor Zainab¹, Syed Ibrahim Hassan²,
Mohammed Mohiuddin³ and Aleem Ahmed Khan⁴**

1. Student of Doctor of Pharmacy (Pharm D), Deccan School of Pharmacy, India
2. Dept. of Gastroenterology Princess Esra Hospital, Hyderabad, India.
3. Dept. of Pharmacology at Deccan School of Pharmacy, Hyderabad, India
4. Central Research Lab, OHRC, Princess Esra Hospital, Hyderabad, India.

Manuscript Info

Manuscript History

Received: 15 December 2020

Final Accepted: 18 January 2021

Published: February 2021

Key words:-

Step up Approach, Tacrolimus (TAC),
Corticosteroid (CS), Inflammatory
Bowel Disease (IBD)

Abstract

Background:-The aim of the study is to compare and evaluate the efficacy and safety of short-term outcomes of tacrolimus in inflammatory bowel disease (IBD) patients who were not concomitantly receiving other immunosuppressive therapies by carrying out an observational prospective study of tacrolimus (TAC) v/s corticosteroid (CS) therapy in the treatment of IBD in active phase, to prevent patient from long term use of CS by reducing the incidence rate of flare. To use TAC as a step-up approach in IBD by early induction of remission and maintain it for longer period which reduces re-hospitalization and surgery rate hence improving quality of life.

Method And Material:-The study was conducted in gastroenterology department, Princess Esra hospital, Hyd. 50 patients were enrolled based on our inclusion and exclusion criteria, allocated in 2 groups receiving CS and TAC respectively for 10 days. Follow-ups were done and at the end of 2 months, again a colonoscopy was performed to assess the effectiveness of the treatment.

Results:-At an initial therapy of 2 months, clinical remissions were observed in most of the patients of both the groups. After six months of treatment, TAC showed 100% remission rate while 20% patients on CS have shown flare.

Conclusion:-prolongs period of remission, and prevents the long-term use of CS thereby preventing its complications proving step-up to be a better approach towards the management of IBD. This study concludes that the efficacy and safety profile of TAC was overall favorable, and the doses were well tolerated by most of the patients.

Copy Right, IJAR, 2021,. All rights reserved

Introduction:-

Inflammatory Bowel Diseases (IBD) are a group of autoimmune diseases characterized by the chronic inflammatory process of both large and small intestine in which body's own immune system attacks the elements of the gastrointestinal tract^[1]. IBD incidence and prevalence rates have increased over the last three decades^[2].

Corresponding Author:- Zeba Samreen

Address:- Student of Doctor of Pharmacy (Pharm D), Deccan School of Pharmacy, India.

The exact etiology of IBD is not well known^[1]. Role of ethnic-racial differences, kinship, effect in twins, chromosomal relationships, hereditary and genetic factors, as well as genetic syndromes are some of the factors associated with IBD. Changes in the content of the gut flora or the disruption of the epithelial function might lead to the pathologic response in the normal mucosal system^[4]. Studies have shown that there is dietary effect on the disease. Newly diagnosed cases consumed more refined sugar and less raw fruit and vegetables when compared to healthy individuals^[5]. The inflammation of the intestinal mucosa in IBD is due to influx of neutrophils and macrophages that produce proteolytic enzymes, cytokines, and free radicals that result in ulceration^[6].

The diagnostic tests include endoscopy, colonoscopy, barium meal follow-through procedure, blood tests, bio markers like ASCA, pANCA (differentiates UC from CD), X-rays, computed tomography and magnetic resonance imaging scans, biopsies of the colon^[1].

Treatment of IBD includes induction and maintenance of remission. The choice of pharmacological therapy is based on severity and location of the disease, efficacy and potency of the drugs, and the desire to minimize the adverse effects of the medication. Currently available pharmacological therapy includes amino salicylate, CS, immunosuppressant, antibiotics and biologic agents^[8].

TAC is macrolide antibiotic, used for prevention of allograft rejection in organ transplantation^[11]. It is a calcineurin inhibitor, immunosuppressive agent which is 10-100 times more potent in inhibiting lymphocyte activation than other immunosuppressant and shown to be safe and effective treatment option for IBD (fistulizing in CD, refractory UC and extra intestinal complications like pyoderma gangrenosum)^[12, 13].

TAC functions by blocking the enzyme calcineurin, thereby interrupting signal transduction in T lymphocytes. Specifically, it inhibits transcription of the first activation genes for interleukin-2 (IL-2), tumor necrosis factor-alpha (TNF- α), and interferon-gamma (IFN- γ). Because of its functional resemblance to cyclosporin-A (CsA), the clinical experience with TAC has mostly been in the steroid dependent or steroid-refractory population of IBD patients. Tacrolimus has enhanced oral bioavailability therefore an oral dose response is more predictable, and IV administration is avoided^[11]. The absorption of TAC is not dependent on mucosal integrity therefore less variability in absorption is observed when compared to CsA^[10].

Material And Methods:-

Institutional review board approval and the informed consent forms were obtained before subject enrollment and data collection.

Study Design:

We carried out an observational Prospective study conducted on patients admitted in gastroenterology department, Princess Esra hospital, Hyderabad within a duration of six months. A total of 50 patients were enrolled based on our inclusion and exclusion criteria allocated in two groups i.e., group I (25 patients) received CS whereas group II (25 patients) received TAC. Both the groups received ASA concomitantly.

Inclusion Criteria:

1. Patients belonging to age above 18 years of both the genders were included.
2. The disease severity must be moderate to severe based on diagnostic tests, Mayo endoscopic scoring system (>5) and Crohn's disease activity index (>220).
3. Patient who are willing to participate in the study were included.

Exclusion Criteria:

1. Patients who have undergone surgeries related to GIT.
2. Patients with comorbid conditions like renal and hepatic abnormalities, uncontrolled diabetes and uncontrolled hypertension, tuberculosis, malignancies.
4. Patients who are on corticosteroids or immunosuppressive therapy six months prior to admission.
3. Pregnant and lactating women.

Study Design:

Patient data was collected from treatment chart, case sheets, during ward rounds and patient data collection form which contain co-morbid conditions, past medical and medication history, Family history, Laboratory data, colonoscopy reports, present medication list, Mayo score chart and CDAI score chart.

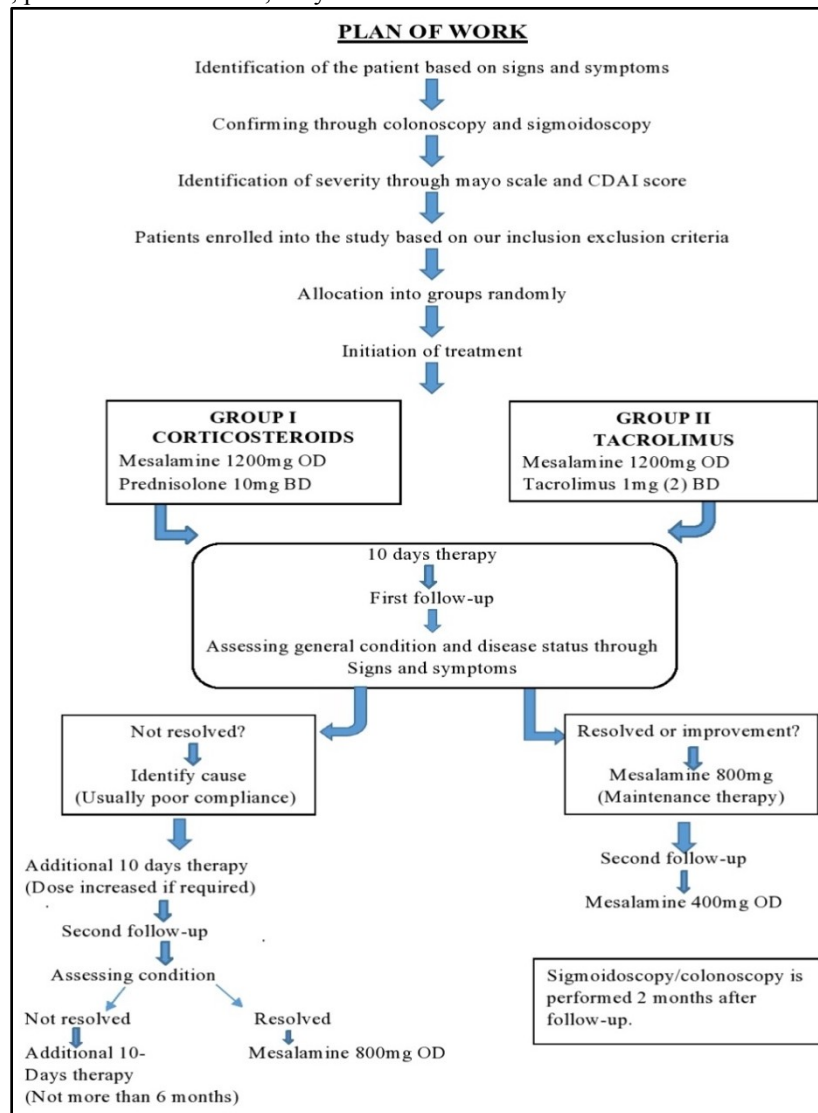


Figure 1:- Plan of work.

Funding:

The authors have no relevant financial or non-financial interests to disclose.

Feasibility:

It is feasible as the study involves the observation on ongoing therapy and hence non-interventional.

Statistical Analysis:

Data was analyzed and the results on continuous variables were calculated by using independent t test. Comparative analysis was performed using chi-square test for categorical variables. Statistical evaluation was performed using SPSS 20.0 version.

Results:-

Most of the patient belonged to the age group of 18-30 years and 51-60 years. In all, 24 UC and 26 CD patients were identified.

In all, 13/24 UC and 12/26 CD patients were on steroids; 11/24 UC and 14/26 CD patients were on tacrolimus. Patients in the study had hypertension (17/50), diabetes (11/50), hypothyroidism (4/50) as comorbidity. Most the patients seemed to have a mixed diet (90%) while few were vegetarians (10%).

The risk factors identified included smoking (6), alcohol (4), genetics (3), and gutka (7). Bristol Stool Scale is used to assess the stool pattern of the patient. In the study, constipated (32%), ideal stool (14%), diarrhea (54%) was found. Based on that, for severe constipation, additional stool softeners were added to the therapy.

After two months of treatment, the severity was assessed again and in both the groups the patient entered remission phase. During the study period, 5/25 i.e., 20% patients of steroid group have shown flare.

At the time of admission, patients in CS group were diagnosed with anemia (7), arthralgia (9), bowel obstruction (2), hemorrhoids (7), anal fissures (5), pseudo polyps (2) and in TAC group, anemia (11), arthralgia (5), bowel obstruction (10), hemorrhoids (8), anal fissures (12), pseudo polyps (2) based on the lab tests.

All the patients were checked on medication adherence and most of them were high adherers based on Morisky scale with 4/25 as medium adherer, 21/25 as high adherer in CS group whereas in TAC group, 2/25 as medium adherer, 23/25 were high adherers.

In the course of study, no patient on TAC while 20% on CS were re hospitalized.

There were no opportunistic infections identified, no cases of renal insufficiency related to drug administration. During the tacrolimus treatment, the serum creatinine and glucose levels were not significantly elevated. No deaths were observed while on therapy.

Adverse Drug Reaction:

Adverse reactions were generally mild. Documented clinical reactions that were thought to be related to TAC included Abdominal pain (3), arthralgia (3), Burping (3), Hair fall (2), Headache (4), Muscle weakness (4), Nausea (3), Rhinitis (4).

Clinical reactions that were thought to be related to CS were Abdominal pain (4), arthralgia (5), body fluid retention (2), Burping (2), Cough (1), Hair fall (1), Headache (1), Insomnia (1), Mouth dryness (1), Muscle weakness (4), Nausea (7), Peripheral edema (1), Rhinitis (1).

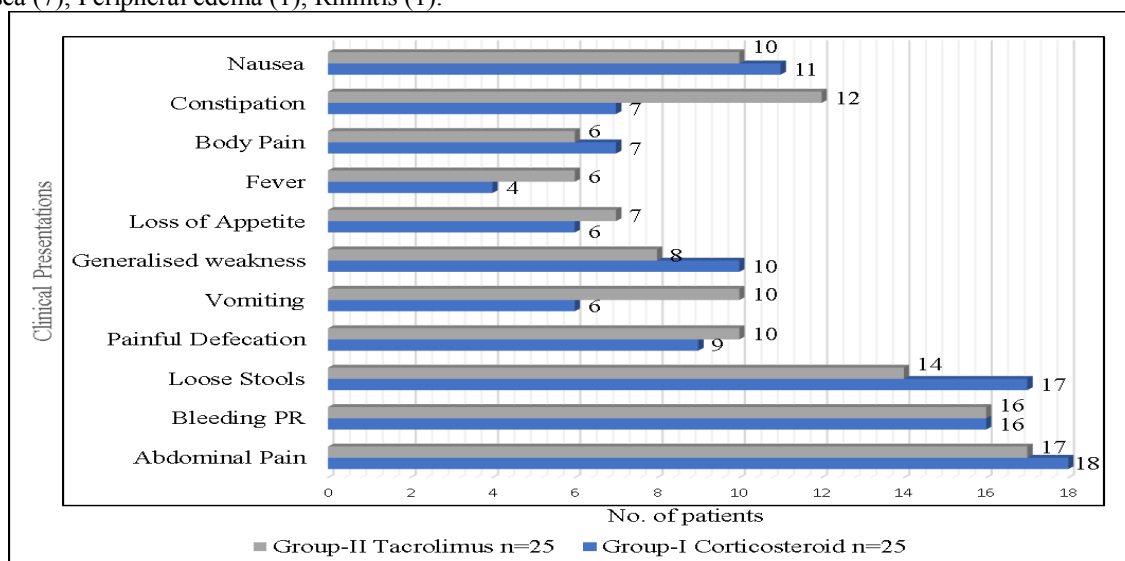


Fig2:- Distribution of patients based on Clinical Presentation at the time of admission

Table 1:- Distribution of patients based on symptomatic treatment.

Medication	Group I Corticosteroids (n=25)	Group II Tacrolimus (n=25)
5-aminosalicylates	25	25
Analgesics	12	13
Anti-emetics	23	25
Anti- hypertensive	10	7
Antibiotics	25	25
Antipyretic	4	6
Corticosteroid (CS)	25	0
Hypo-glycaemic	7	4
Iron supplements	7	8
Laxatives	9	12
Nutritional supplements	22	21
Opiates	1	7
PPI/ H2RA	25	25
Probiotics	16	17
Tacrolimus (TAC)	0	25
Thyroid hormone	4	0

Table 2:- Serological tests and Colonoscopy report of patients before and after treatment of Group I.

CORTICOSTEROID						
SNo.	GENDER	AGE	SEROLOGICAL TEST		COLONOSCOPY REPORT	
			ASCA IgA	ASCA IgG	AT ADMISSION	AFTER TWO MONTHS
1	male	60	negative	negative	MU with MC and E at R, SC, DC.	normal study
2	female	45	positive	positive	PP-2-degree INH, MU with NIM at R, SC, DC, TC.	PP-2-degree INH, Normal study
3	male	26	positive	negative	MU in R,MC& E at SC, DC, Fissure in Ano	normal study
4	female	38	positive	positive	MU with MC and E at R, SC	early remission phase
5	female	30	negative	negative	PP-2-degree INH,MU with NIM at SC,DC,TC,AC.	PP-2-degree INH, normal study
6	female	51	negative	negative	MU with MC & E at R, SC, DC.	Normal study with inter gluteal erosions
7	female	54	positive	positive	PP-2-degree INH, MU with NIM at R,SC,DC	PP-2-degree INH, normal study
8	female	65	negative	negative	MU with MC & E at R, SC, DC.	U at HP, normal study
9	female	36	negative	negative	MU with MC & E at DC, TC.	normal study
10	female	65	negative	negative	PP-2-degree INH, MU with MC & E at R, SC, DC.	PP-2-degree INH, Normal study
11	male	52	positive	positive	MU with MC and E with SA in R, SC, DC, TC	Normal study
12	female	18	positive	negative	MC & E at R, SC, Fissure in Ano.	U at HP, normal study

13	female	55	negative	negative	MU with NIM at R	Normal study
14	female	60	positive	negative	MU with MC & E at R, SC, Pedunculated polyp at R.	normal study
15	female	65	negative	negative	PP- 1-degree INH, MU with clots over it extending up to ano-rectal junctions at R, MU with MC at SC, DC	PP- 1-degree INH, Normal study
16	female	60	negative	negative	PP- 1-degree INH, MU with MC and E at R, SC	PP- 1-degree INH, Normal study
17	female	30	negative	negative	MU with MC & E at R, SC, DC.	normal study
18	male	50	positive	negative	MU with NIM at R, SC.	normal study
19	male	90	positive	negative	MU with NIM at R, SC.	normal study
20	male	18	negative	negative	MU with MC and E in R, MU with NIM at SC.	normal study
21	female	28	positive	positive	MU with NIM at R, SC	MU with small pinpoint U at R, Normal study
22	female	34	negative	negative	PP-2-degree INH, MU with MC and E at R	Thrombosed INH, Normal study
23	male	25	positive	positive	MU with MC and E at R, SC, DC, fissure at ano	U at HP, normal study
24	male	18	positive	positive	PP-2-degree INH, MU at R, UPP at SC.	PP-2-degree INH, Normal study
25	male	40	negative	negative	MU with MC and E in R, MU with NIM at SC.	normal study

NIM-normal intervening mucosa, U- Ulcers, MU- multiple ulcerations, MC- mucosal congestion, E- edema, SA- skip areas, R- rectum, SC- sigmoid colon, DC- Descending colon, TC- transverse colon, AC- Ascending colon, CCJ- caecum colon junction, TI- Terminal ileum, INH- internal hemorrhoids, PP- Proctoscopy position, HP- Healing phase, C-Caecum

Table 3:- Serological tests and Colonoscopy report of patients before and after treatment of Group II.

TACROLIMUS						
SNo.	GENDER	AGE	SEROLOGICAL TEST		COLONOSCOPY REPORT	
			ASCA IgA	ASCA IgG	AT ADMISSION	AFTER TWO MONTHS
1	female	65	negative	negative	PP- 2-degree INH, MU with NIM at R, SC	PP- 2-degree INH, Normal study
2	male	62	positive	negative	PP-2-degree INH, MU with NIM at R, SC, DC, TC. Pseudo polyp at SC, TC, Fissure in Ano	PP-2-degree INH, Pseudo polyp at TC, U at HP, Normal Study

3	male	40	positive	negative	PP-2-degree INH, MU with MC at R, DC.	PP-2-degree INH, Normal Study
4	male	40	negative	negative	MU with MC & E at R, SC.	normal study
5	female	45	positive	positive	PP-2-degree INH, MU with NIM at R, SC.	PP-2-degree INH, normal study
6	female	21	positive	negative	MU with NIM at TC, AC.	U at HP at TC, AC, Normal study
7	female	19	negative	negative	MU with MC & E at R, SC, Fissure in Ano	normal study
8	male	49	positive	positive	MU with NIM at R, SC, DC, TC. Pseudo polyp at DC	Pseudo polyp at DC, Normal study
9	male	34	negative	negative	MU with MC & E at R, SC, Fissure in Ano	normal study
10	female	72	negative	negative	MU with MC & E at R, SC, Fissure in Ano	U-HP with NIM at R, SC.
11	female	33	positive	negative	MU at R, Fissure in Ano	normal study
12	male	22	positive	negative	MU with NIM at R, SC, DC, TC, AC, C.	normal study
13	male	28	negative	negative	MU with MC & E at R, SC, Fissure in Ano	normal study
14	male	55	positive	negative	MU with NIM at SC, TC, AC, Fissure in Ano	normal study
15	male	55	positive	negative	MU at R.	normal study
16	male	50	negative	negative	MU with NIM at R, SC	normal study
17	male	34	positive	negative	MU at R, SC	U-HP at R, SC.
18	male	65	positive	negative	PP-2 degree INH, MC& E at R,SC.	PP-2-degree INH, U at HP, Normal Study

19	male	28	negative	negative	MU with MC & E at R, SC, Fissure in Ano	normal study
20	male	48	positive	negative	PP-1-degree INH, MU with NIM at R, SC, Fissure in Ano	PP-1-degree INH, Normal Study
21	male	62	positive	positive	MU with NIM at AC, C.	normal study
22	female	23	positive	positive	MU with MC & E at R, SC.	U at HP, normal study
23	female	72	positive	negative	MU with MC & E at R, SC, Fissure in Ano	normal study
24	female	42	negative	negative	PP-2-degree INH, MU with MC & E at R, SC, DC.	PP-2-degree INH, Normal Study
25	male	26	negative	negative	PP-1-degree INH, MU with NIM at SC	PP-1-degree INH, Normal Study

Table 4:- Severity assessment based on scales. P value was found to be <0.05 which is statistically significant.

Before Treatment In UC					After Treatment In UC				
Group	Mayo score			P value	Group	Mayo score			P value
	Mild (3-5)	Moderate (6-10)	Severe (11-12)			Mild (3-5)	Moderate (6-10)	Severe (11-12)	
Group I	0	12	1	0.22	Group I	1	0	0	0.04
Group II	0	9	2		Group II	0	0	0	
Total UC Patients n=24(100%)	0 (0%)	21 (87.5%)	3 (12.5%)		Total UC Patients n=24(100%)	1 (4%)	0 (0%)	0 (0%)	
Before Treatment In CD					After Treatment In CD				
Group	CDAI score			P value	Group	CDAI score			P value
	Mild (150-219)	Moderate (220-450)	Severe (above 450)			Mild (150-219)	Moderate (220-450)	Severe (above 450)	
Group I	0	7	5	0.05	Group I	2	0	0	0.02
Group II	0	9	5		Group II	0	0	0	
Total CD Patients n=26	0 (0%)	16 (61.5%)	10 (38.5%)		Total CD Patients n=26	2 (7.7%)	0 (0%)	0 (0%)	

Discussion:-

IBD incidence and prevalence rates have increased over the last three decades. Within first five years after the diagnosis of the disease, about one third of the patients have had intestinal surgery ^[2]. The burden of the disease is rising globally, with considerable difference in levels and trends of disease in different countries and regions ^[3].

During the course of study, 57 patients were admitted in gastroenterology department of Princess Esra hospital in a span of six months i.e., from Aug 2019 to Jan 2020. 6 patients did not meet our inclusion criteria and 4 patients were lost to follow up therefore making a sample size of 50 patients who were randomly allocated into two groups after performing serological test, colonoscopy and assessing the severity. Sample collection ended in December and patients were followed up till 6 months from the date of admission.

IBD have bimodal or trimodal distributions in age of presentation of disease. The first peak occurs in 20 and 39 years, and a second peak between 50 and 80 years ^[16]. It is a lifelong disease occurring in both the genders, but the ratio of women is slightly greater ^[2]. It was noted in our study that most patients belonged to age groups of 18-30 and 51-60. The male and female ratio was equal but due to small sample size, a conclusion cannot be drawn.

We evaluated the clinical presentations, management patterns and outcomes in the patients. Most of the patients were admitted with chief complaints of severe abdominal pain, bleeding per rectum, loose stools along with nausea, constipation, body pain, fever, loss of appetite, generalized weakness, vomiting and painful defecation. Some of the clinical symptoms of this disease are pain in abdomen, vomiting, fever, constipation, diarrhea mixed with blood, arthritis, weight loss and anemia ^[6]. Some of the other diagnostic features seen in our study at the time of admission were anemia, arthralgia, bowel obstruction, hemorrhoids, anal fissures, pseudo polyps based on the lab tests.

Factor like smoking seemed to have an impact over an increased risk of developing IBD and with increased risk of flares ^[2]. In our study, we found 6 smokers, 4 alcoholics, and 7 patients consumed gutka. Three people in the study seemed to be genetically related to IBD patients indicating genetic factor.

Several Comorbid health conditions such as diabetes, heart disease, cancer, psychiatric disorders and arthritis are commonly present in elderly patients with IBD. This contributes to a higher risk of complications and mortality after a severe attack of UC or CD in advanced age ^[7]. In our study, 17 patients had hypertension, 11 had diabetes and 4 patients had hypothyroidism. Patients who had cancer were excluded from the study.

Oral/ topical Mesalamine and CS are generally used as starting therapy for mild to moderate UC, whereas systemic CS and biologicals are more often used in moderate/severe forms of IBD ^[7]. TAC taken after 10hrs of fasting, 1hr after meal or 2hrs after meal showed higher serum levels when compared to taken immediately after meal or within 1.5hrs after meal concluding food delays absorption of the drug ^[14]. TAC is a narrow therapeutic drug therefore therapeutic drug monitoring is necessary.

ADR's of TAC includes tremors, GI discomfort, kidney injury, infections ^[11, 14]. Patients on CS were observed with ADR's like osteoporosis, pathological fractures, cataract, metabolic changes, acne, striae, and hirsutism ^[10]. Adverse reactions observed in our study were generally mild as the drug was given only for short period.

In our study, both the groups were given 5- amino salicylates. TAC was administered orally in 25 patients at a dose of 0.1 mg/kg bodyweight per day i.e., two tablets of 1mg, twice daily till 10 days. CS (prednisolone) was administered to 25 patients at a dose of 10mg BD for 10 days. After 2 months, patients were called for follow up to perform colonoscopy and severity was assessed based on Mayo endoscopic scoring system and Crohn's disease activity index (CDAI). Results in both the groups was similar i.e., all the patients entered into remission phase after the initial treatment. Within 6 months after the admission, 5 patients in CS group whereas no patient in TAC group have shown a flare and were re-hospitalized. This points out that TAC prolongs the period of remission when given in the active phase for short duration of time. In short term use, after 7 days of therapy, target blood concentration is reached. In long term use, found in various meta-analysis, 62% patients who received TAC have shown colectomy free survival rate at 65 months of initial therapy ^[10].

All the patients were checked on medication adherence and most of them were high adherers based on Morisky's scale. For 10 days, we noted down changes in vitals, blood pressure, blood glucose, LFT, CBP, RFT on all the

patients in our study. No significant changes were noted suggesting that both the drug doses were well tolerated, and no deaths were observed while on therapy.

Studies have shown that a top-down approach, in which a potent agent is started at the early stage or active phase inpatients with moderate to severe IBD, such as an aggressive treatment with anti-TNF agents and immunosuppressant like TAC and patients not receiving concomitant steroid therapy may be associated with reduced hospitalization and surgeries in IBD patients, which compensate the lower cost of traditional therapies [7, 15].

Prednisone given at a dose of 60 mg daily is found to be effective in initial management of moderately to severely active CD and UC to induce remission. The dose had to be tapered over 3-6 weeks or can be discontinued based on the patient responding to the drug. It was seen that 20% patients in UC require several courses of CS which leads to increased drug related complications before a stable remission is observed [9].

Conclusion:-

Two months after the therapy, clinical remissions were observed in most of the patients. In the study duration, clinical remissions were maintained in all the patients those were on tacrolimus i.e., 100% and 80% patients those were on corticosteroids suggesting TAC prolongs period of remission thus preventing the long-term use of CS and need of surgeries related to GIT.

This concludes that the efficacy and safety profile of tacrolimus was overall favorable, and the doses were relatively well tolerated by most of the patients. Therefore, oral TAC as an accelerated step up or top-down therapy appears to be a viable option for short term treatment in moderate to severe cases of IBD in active phase.

Limitations:-

The duration of the study was only for 6 months and bulk patients could not be taken into the study therefore there was a small sample size of only 50 patients.

We were not able to follow-up the remission period after 6 months.

Conflict Of Interest:

All authors have no conflict of interest

Author Contributions:

All authors participated sufficiently, intellectually or practically, in the work to take public responsibility for the content of the article, including concept, design, data interpretation and writing of the manuscript was approved by all the authors.

Declaration:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board (IRB) Deccan College of Medical Sciences and Allied Hospitals, Hyderabad, India.

References:-

1. Fakhoury, M., Al-Salami, H., Negrulj, R., & Moorianian, A. (2014). Inflammatory bowel disease: clinical aspects and treatments. *Journal of Inflammation Research*, 113. <https://doi.org/10.2147/jir.s65979>
2. Hovde, Ø. (2012). Epidemiology and clinical course of Crohn's disease: Results from observational studies. *World Journal of Gastroenterology*, 18(15), 1723. <https://doi.org/10.3748/wjg.v18.i15.1723>
3. Alatab, S., Sepanlou, S. G., Ikuta, K., Vahedi, H., Bisignano, C., Safiri, S., Sadeghi, A., Nixon, M. R., Abdoli, A., Abolhassani, H., Alipour, V., Almadi, M. A. H., Almasi-Hashiani, A., Anushiravani, A., Arabloo, J., Atique, S., Awasthi, A., Badawi, A., Baig, A. A. A., ... Naghavi, M. (2020). The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Gastroenterology & Hepatology*, 5(1), 17–30. [https://doi.org/10.1016/s2468-1253\(19\)30333-4](https://doi.org/10.1016/s2468-1253(19)30333-4)
4. Heyman, M. B., Kirschner, B. S., Gold, B. D., Ferry, G., Baldassano, R., Cohen, S. A., Winter, H. S., Fain, P., King, C., Smith, T., & El-Serag, H. B. (2005). Children with early-onset inflammatory bowel disease (IBD): Analysis of a pediatric IBD consortium registry. *The Journal of Pediatrics*, 146(1), 35–40. <https://doi.org/10.1016/j.jpeds.2004.08.043>

5. Thornton, J. R., Emmett, P. M., & Heaton, K. W. (1979). Diet and Crohn's disease: characteristics of the pre-illness diet. *BMJ*, 2(6193), 762–764. <https://doi.org/10.1136/bmj.2.6193.762>
6. Guan, Q. (2019). A Comprehensive Review and Update on the Pathogenesis of Inflammatory Bowel Disease. *Journal of Immunology Research*, 2019, 1–16. <https://doi.org/10.1155/2019/7247238>
7. Arnott, I., Rogler, G., & Halfvarson, J. (2017). The Management of Inflammatory Bowel Disease in Elderly: Current Evidence and Future Perspectives. *Inflammatory Intestinal Diseases*, 2(4), 189–199. <https://doi.org/10.1159/000490053>
8. Management of patients with inflammatory bowel disease: current and future treatments. (2017). *Clinical Pharmacist*. <https://doi.org/10.1211/cp.2017.20202316>
9. Naganuma, M., Fujii, T., & Watanabe, M. (2010). The use of traditional and newer calcineurin inhibitors in inflammatory bowel disease. *Journal of Gastroenterology*, 46(2), 129–137. <https://doi.org/10.1007/s00535-010-0352-z>
10. Baumgart, D. C., Pintooff, J. P., Sturm, A., Wiedenmann, B., & Dignass, A. U. (2006). Tacrolimus Is Safe and Effective in Patients with Severe Steroid-Refractory or Steroid-Dependent Inflammatory Bowel Disease-A Long-Term Follow-Up. *The American Journal of Gastroenterology*, 101(5), 1048–1056. <https://doi.org/10.1111/j.1572-0241.2006.00524.x>
11. Benson, A., Barrett, T., Sparberg, M., & Buchman, A. L. (2008). Efficacy and safety of tacrolimus in refractory ulcerative colitis and Crohn's disease: A single-center experience. *Inflammatory Bowel Diseases*, 14(1), 7–12. <https://doi.org/10.1002/ibd.20263>
12. Faubion, W. A., Loftus, E. V., Harmsen, W. S., Zinsmeister, A. R., & Sandborn, W. J. (2001). The natural history of corticosteroid therapy for inflammatory bowel disease: A population-based study. *Gastroenterology*, 121(2), 255–260. <https://doi.org/10.1053/gast.2001.26279>
13. KhurramBaig, M., Marquez, H., Noguera, J. J., Weiss, E. G., & Wexner, S. D. (2004b). Topical tacrolimus (FK506) in the treatment of recalcitrant perianal pyoderma gangrenosum associated with Crohn's disease: report of two cases. *Colorectal Disease*, 6(4), 250–253. <https://doi.org/10.1111/j.1463-1318.2004.00607.x>
14. Bekersky, I., Dressler, D., & Mekki, Q. (2001). Effect of Time of Meal Consumption on Bioavailability of a Single Oral 5 mg Tacrolimus Dose. *The Journal of Clinical Pharmacology*, 41(3), 289–297. <https://doi.org/10.1177/00912700122010104>
15. Inoue, T., Murano, M., Narabayashi, K., Okada, T., Nouda, S., Ishida, K., Kawakami, K., Abe, Y., Takeuchi, T., Tokioka, S., Umegaki, E., & Higuchi, K. (2013). The Efficacy of Oral Tacrolimus in Patients with Moderate/Severe Ulcerative Colitis Not Receiving Concomitant Corticosteroid Therapy. *Internal Medicine*, 52(1), 15–20. <https://doi.org/10.2169/internalmedicine.52.8555>
16. Garland, C. F., Lilienfeld, A. M., Mendeloff, A. I., Markowitz, J. A., Terrell, K. B., & Garland, F. C. (1981). Incidence Rates of Ulcerative Colitis and Crohn's Disease in Fifteen Areas of the United States. *Gastroenterology*, 81(6), 1115–1124. [https://doi.org/10.1016/s0016-5085\(81\)80021-2](https://doi.org/10.1016/s0016-5085(81)80021-2)