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Infliximab and Mesalazine in Inflammatory Bowel Disease: A comparative clinical Study

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Abstract:
Aim: *To compare the role of Infliximab and Mesalazine in patients with Inflammatory Bowel Disease.*
Methods:30 IBD patients were included in the study.15 patients (Group A) were treated with Infliximab 5mg/kg i.v and 15 patients (Group B) were treated with Mesalazine 2.4g/day orally.Both the drugs were administered for one year.
Result: *Out of total 30 patients all patients of Group A achieved no of stools < 2 after 12 months therapy where as it is only 10 patient in group B.It is observed that there is more improvement in all the different parameters at 1month,6 month and 12month with infliximab therapy in comparision to mesalazine therapy.*
Conclusion: *Infliximab observed to give better response in comparision to Mesalazine in the treatment of Inflammatory Bowel Disease.*
Keyword: *Inflammatory Bowel Disease,Tumor Necrosis Factor,Infliximab,Mesalazine*

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I. Introduction

Inflammatory bowel disease (IBD),including ulcerative colitis(UC) and Chron's disease(CD),are chronic disabling and progressive disorders characterized by life long treatment and whose incidences are increasing in Asia.(1,2,3,4)Although the etiology of IBD remains unclear,the pathogenesis of IBD has been recently advanced.It is strongly suggested that altered immunological function,resulting from an interplay between genetic susceptibility and certain environmental factors including bacterial infection,contribute to the development of mucosal inflammatory responses of gastrointenstinal tract.(5)Proinflammatory cytokines,especially tumor necrosis factor (TNF),are produced mainly by activated immune cells in inflamed mucosa during the process of IBD, and those proinflammatory cytokines futher activate immune cells to produce toxic molecules including super oxygen products,chemokines,proteinases and cytokines which result in tissue damage and inflammation development.(6,7)Inflammatory bowel disease groups together two distinctive clinical entities:UC and CD.These two diseases differ in their location(colon only for UC and the whole length of the intenstinal tract for CD),pattern of distribution (continuous vs patchy),depth of involvement(mucosal vs transmural) and histology (crypt abcesses vs granulomas).The pathogenesis of IBD has been hypothesized to be caused by an inappropriate immune response against luminal antigen in a genetically susceptible host resulting in uncontrolled intenstinal inflammation.(8)CD has been traditionally described as a Th 1 mediated disease with predominant cytokines being the pro-inflammatory cytokines INF ϒ,IL-1β and IL-12.These cytokines contribute to an increase in mucosal permeability,collagen synthesis and recruitment of inflammatory cells.(9)UC,on the other hand,has been considered to be an atypical Th2 mediated disease characterized by CD4+ T lymphocytes bearing a natural killer(NK) T lymphocyte marker.Levels of IL-4,IL-5,IL-8 but also IL-1β,IL-12 and IFN gamma are significantly higher in patients with UC than in healthy controls.(10)The conventional treatments of IBD include corticosteroids and aminosalicylates.However only 50% of patients achieve sustained remission with the conventional drugs which can raise many side effects.(11)Recently many novel drugs have been developed for clinical IBD management and among them TNF neutralization by monoclonal antibodies has been shown as one of the effective approaches for IBD treatment.(12)TNF-α is a cytokine involved in inflammatory responses and is a member of the TNF-superfamily.It is capable of killing tumor cells in vitro and causing hemorrhagic necrosis of transplantable tumors in mice.(13)Monocytes/macrophages are the main source of TNF-α although T and B lymphocytes also produce significant amounts.Other cells known to produce TNF-α include NKcells,mast cells,Paneth cells,keratinocytes,astrocytes and microglial cells,smooth muscle cells,and certain tumor cell lines.(14)Infliximab is a chimeric anti-TNF-α mouse monoclonal antibody.(15)Its Fab fragment consists of the mouse variable TNF binding region(25% of the protein) and a human Fc fragment (75% of the protein).(16)

The mechanism of action of infliximab is not clearly understood.Although initially thought to be mediated via neutralization of soluble TNF-α,this is clearly not enough because treatment with other anti-TNF-α antibodies and soluble TNF-α receptors with similar or even greater neutralizing efficacy do not exert the same therapeutic effect.Recent investigations suggest that the mechanism of action of TNF-α-blocking agents is mediated via apoptosis of TNF-α-expressing inflammatory cells.These studies suggest that mucosal T cells of patients with IBD are highly resistant to apoptosis.(17)It is administered intravenously at a dose of 5 or 10 mg/kg.The temporal regimens employed in IBD include administration on weeks 0,2, and 6 and then periodically every 8 weeks.(18)In the intenstine,the direct effects of TNF-α on intenstinal epithelium include disruption of the epithelial barrier,induction of apoptosis of epithelial cells, and secretion of chemokines from intenstinal epithelial cells.TNF-α also activates the adaptive immune system of the bowel through recruitment and activation of neutrophils and macrophages.(14)Sulfasalazine was originally developed to deliver both antibacterial (sulfapyridine) and anti-inflammatory (5-aminosalicylic acid,ASA) agents into the colon mucosa.In the lumen,sulfasalazine is split into sulfapyridine and 5-ASA(mesalazine) by colonic bacteria by means of an azoreductase.But the liberated sulfapyridine is responsible for many undesirable side effects like headache,anorexia,nausea and vomiting there by limiting the usage of sulfasalazine.Salicylazosulphapyridine is a conjugate of 5-aminosalicylate and sulfapyridine.

5-aminosalicylate was identified as the principal effective component of this conjugate in the 1970s.(19,20) and remains the starting point for the clinical use of monocomponent 5-aminosalicylate or mesalazine.Although the exact mechanism of action of mesalazine has still to be elucidated.(21,22)Several potential mechanism have been suggested,including 5-aminosalicylate-induced inhibition of inflammation by interfering with the metabolism of arachidonic acid,prevention of mucosal generation of leukotrienes and prostaglandins,scavenging of free radicals.(23,24) and mechanisms only recently identified involving inhibition of nuclear factor-kappaB and induction of apoptosis.(25-29)

5-aminosalicylate is believed to act in the damaged epithelial intenstinal layer,where it is transformed into the inactive acetylated 5-aminosalicylate,which is subsequently filtered and excreted by the kidneys.As a result,the therapeutic activity and efficacy of 5-aminosalicylate are related to its intraluminal concentration.(30)

With the advances in the understanding of the pathological mechanisms involved in IBD,new therapies have been proposed,with the most important development being the introduction of anti-tumor necrosis factor(TNF) agents.(31,32)Anti-TNF agents (infliximab,adalimumab,and cetrolizumab) have reduced the need for surgery and hospitalization and have improved the quality of life of patients by changing the course of the disease.(33,34)Thus guidelines recommend the use of anti-TNF agents initially in moderate-to-severe IBD or if non-biological therapy fails.(35,36,37,38) Infliximab is administered as an intravenous infusion of 5mg/kg at weeks 0,2,6 and every 8 weeks thereafter.One of the most common adverse effects of infliximab is a flulike infusion reaction,which can be prevented or lessened by the premedication of an antihistamine and paracetamol,with or without a corticosteroid.(39) No difference in efficacy was found between doses of mesalazine of 0.8 and 1.6 g daily.(40)Another study suggested a trend for increased efficacy at higher doses,of 3g/day.(41)This study was undertaken to compare the efficacy between Infliximab and Mesalazine in patients of IBD.

II. Material And Methods

The study was conducted in the department of Gastroenterology Apollo Hospital Bhubaneswar for one year from March 2019 to February 2020.

Inclusion criteria:

1.Induction and maintenance therapy in adult patients with moderate to severe active disease who have had an inadequate response to conventional therapy.

2.Severe,refractory extraintenstinal manifestations:arthritis,pyoderma gangrenosum and iritis/uveitis

Exclusion Criteria:

1.Moderate or Severe HF

2.Active solid or hematological malignancies

3.Untreated latent TB

4.Active systemic infection

Patients were divided into two groups i.e Group:A and Group: B.

In each group 15 patients were included.Group A patients were given infliximab intravenously in the dose of 5mg/kg at 0,2,and 6 wkly for induction therapy and 5mg/kg every 8 weeks for one year maintenance therapy.

Group B patients were administered meselazine orally in the dose of 2.4g/day for one year.

Disease severity and improvement assessment were done by Chron's Disease Activity Index,Harvey Bradshaw Index ,the Perianal Chron's Disease Activity Index and indices for Ulcerative Colitis include the Truelove and Witts severity index and the Sutherland Index.In our study severity of the disease is accessed by Truelove and Witts Severity Index and CD Activity Index (CDAI).The parameters included were Number of

stools per day,Blood in stool,Fever,Tachycardia(>90 beats/min),Anaemia,ESR >30mm/hr,Arthritis or arthralgia,Iritis or uveitis,Anal fissure or fistula or abscess,Body weight.Patients were accessed in 0,1,2,4 weeks intervals.Clinical improvement were also accessed by comparing between Infliximab and Sulfasalazine at 6 and 12 months of drug administration.

Statistical Analysis:
Statistical Analysis was done by applying paired t-test.As there are 30 samples degree of freedom is 29.P value found to be less than 0.05 and the difference observed is significant.

III. Result

Group:A Infliximab therapy (15 patients) Table:1

Parameters	0 day	1 week	2 week	4 week
No of stools per day	>6	4-5	3-4	<2
Blood in stool	+	+	-	-
Fever	+	+	-	-
Tachycardia>90 beats/min	+	-	-	-
ESR>30mm/hr	+	+	+	-
Abdominal pain	+	+	-	-
Arthritis	+	+	-	-
Anal fissure/fistula	+	+	-	-

Group:B Mesalazine therapy (15 patients) Table:2

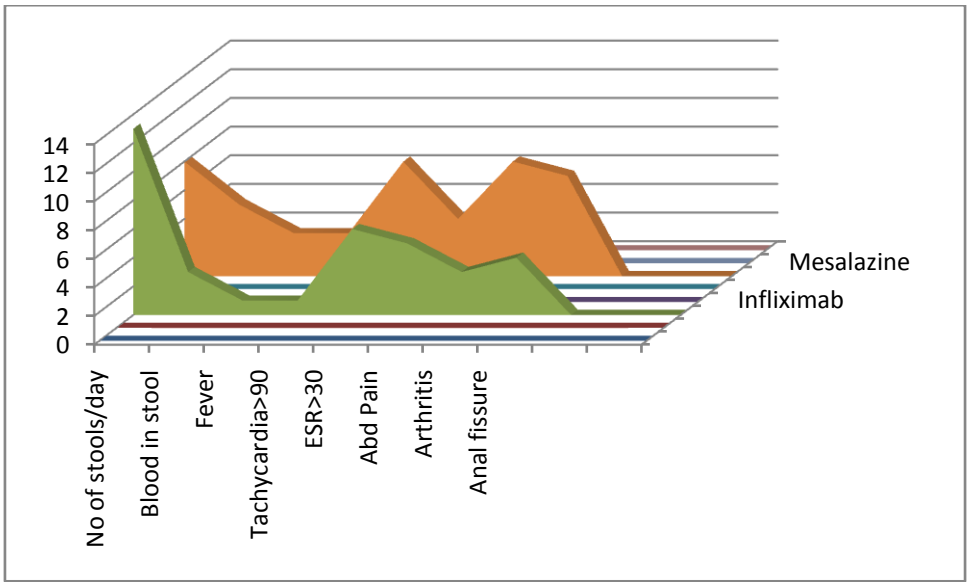
Parameters	0 day	1 week	2 week	4 week
No of stools per day	>6	5-6	4-5	3-4
Blood in stool	+	+	+	+
Fever	+	+	+	-
Tachycardia>90 beats/min	+	+	+	-
ESR>30mm/hr	+	+	-	-
Abdominal pain	+	+	+	+
Arthritis	+	+	+	+
Anal fissure/fistula	+	+	+	-

Group:A Infliximab Therapy(15 patients) Table:3
Response after 1 month of treatment
(Represented in number)

Parameters	Response after 1month of treatment
No of stools per day <2	13
Blood in stool after 1 month	3
Fever	1
Tachycardia>90 beats/min	1
ESR>30mm/hr	6
Abdominal pain	5
Arthritis	3
Anal fissure/fistula	4

Group:B Mesalazine Therapy(15 patients) Table:4
Response after I month of treatment
(Represented in number)

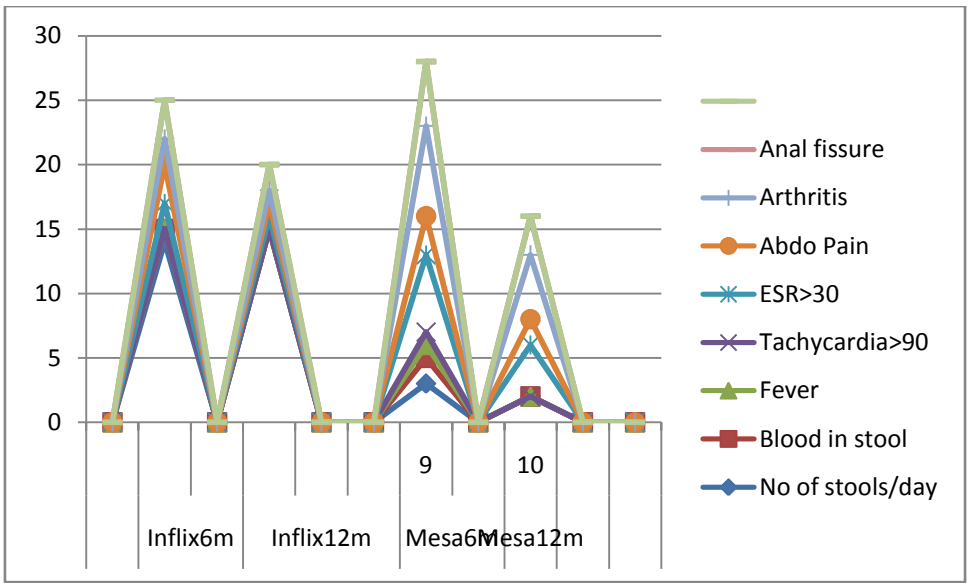
Parameters	Response after 1 month of treatment
No of stools per day <2	8
Blood in stool after 1 month	5
Fever	3
Tachycardia>90 beats/min	3
ESR>30mm/hr	8
Abdominal pain	4
Arthritis	8
Anal fissure/fistula	7



GRAPH-1 Shows comparision in improvement different parameters with Infliximab and Mesalazine therapy after 1month

	Infliximab Therapy		Mesalazine Therapy	
	6 month	12 month	6 month	12 month
No of stools per day	14	15	9	10
Blood in stool	1	0	3	2
Fever	0	0	2	0
Tachycardia>90	0	0	1	0
ESR>30per hour	2	1	6	4
Abdominal Pain	3	1	3	2
Arthritis	2	1	7	5
Anal fissure	3	2	5	3

Comparision of Responses between Infliximab and Mesalazine therapy after 6months and 12 months(Represented in no)



Graph 2 shows the comparision of responses of different parameters between Infliximab and Mesalazine after 6 months and 12 months

From the above tables and Graphs it is seen that there is improvement in all the different parameters at 1month,6 month and 12 months with infliximab therapy in comparision to mesalazine therapy.Only 1 patient was having fever and tachycardia in Group A where as 3 patients were having the same in Group B after one

month of drug administration.No patients were having fever and tachycardia at the end of the study.15 patients from Group A achieved no of stools < 2 after 12 months where it is 10 patients from Group B.No patients having tachycardia in both the groups at the end of the study.Persistence of ESR >30 per hour seen in 4 patients at the end of the study.There is persistence improvement in different parameters seen with infliximab therapy from one month to end of the study in comparision to Mesalazine therapy.

IV. Discussion

In patient with acute symptoms of IBD the goal is to induce clinical remission of symptoms while improving quality of life.(42,43)In addition to clinical symptoms,mucosal healing may also be considered a goal of therapy in IBD.Mucosal healing is associated with an alteration in disease course and natural history for both CD and UC resulting in fewer hospitalizations,reduce need for surgery and lower rates of disease complications.(44,45,46) Mucosal healing has appeared as an important treatment goal for patients with IBD,and can alter the course of IBD with sustained clinical remission and reduced rates of hospitalization and surgical resection.(47)The antibodies against TNF including infliximab and adalimumab induce formation of regulatory macrophages in an Fc region-dependent manner.The induced regulatory macrophages inhibit proliferation of activated T cells,produce anti-inflammatory cytokines, and express the regulatory macrophage marker CD206.(48)

V. Conclusion

The present study also shows significant improvement with infliximab therapy in comparision to mesalazine therapy.All assessment parameters shows better result in infliximab therapy.
Hence it can be concluded from our study that infliximab therapy is better in comparision to mesalazine therapy in treatment of IBD.

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