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Assessment of efficacy of infliximab, Azathioprine, or combination therapy for Crohn's disease

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Abstract
Background: The present study was conducted for assessing the efficacy of Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease.
Materials and Methods: A total of 60 patients with confirmed diagnosis of Crohn's Disease were enrolled. Complete demographic and clinical details of all the subjects was recorded. Random division of all the patients was done into three study groups as follows: Group 1: Azathioprine group, Group 2: Infliximab group and Group 3: Combined therapy. Oral mesalamine was continued at a stable dose. Systemic corticosteroids could be initiated with the dose maintained, increased, or decreased until week 14. The primary efficacy end point was the rate of corticosteroid-free clinical remission at week 26; the rates of corticosteroid-free clinical remission at other time points were secondary efficacy end points. All the results were recorded in Microsoft excel sheet and were analysed by SPSS software.
Results: Mean age of the patients of the Azathioprine group, Infliximab group and Combined therapy group was 43.2 years, 40.7 years and 41.6 years respectively. Major proportion of the subjects of all the study groups were males. Patients with corticosteroid free clinical remission was similar in all the three groups. Patients who received systemic corticosteroids during therapy was also similar in all the three groups. Nausea, vomiting, abdominal pain, worsening of disease, fatigue, headache and arthralgia were the commonly encountered adverse events.
Conclusion: In Crohn's disease patients, infliximab monotherapy and combination therapy with infliximab plus azathioprine, in comparison to azathioprine alone, causes enhanced rates of corticosteroid-free clinical remission.

Keywords: Crohn's disease, azathioprine, infliximab

Introduction
Crohn disease (CD) and ulcerative colitis (UC) are two conditions commonly referred to as inflammatory bowel disease (IBD). They are immunologically mediated inflammatory diseases of the gastrointestinal tract. In CD, the inflammation extends through the entire thickness of the bowel wall from the mucosa to the serosa. The disease runs a relapsing and remitting course. With multiple relapses, the CD can progress from initially mild to moderate inflammatory conditions to severe penetrating (Fistulization) or structuring disease [1, 2].
It is characterized by a transmural granulomatous inflammation which can affect any part of the gastrointestinal tract, most commonly the ileum, colon or both. Its prevalence has continually increased over the past 50 years with the highest incidence being reported in northern Europe, the United Kingdom and North America. Despite biological treatment being associated with an improved health-related quality of life, patients still report significant impediment on lifestyle and daily activities during both flares and remissions. The mortality amongst patients with CD has been persistently higher than the general population with a meta-analysis showing a pooled estimate for the standardized mortality ratio of 1.52 [3, 4]. Among immunosuppressive- and biologic-naïve patients with moderately-to-severely active Crohn's disease (CD), a higher proportion of those treated with the combination of infliximab and azathioprine achieved corticosteroid-free remission at week 26 (CSFR26) than those given infliximab monotherapy; patients given the combination therapy also had higher serum concentrations of infliximab. Enhanced benefit of combination therapy may occur through synergistic modes of action or the influence of azathioprine on infliximab pharmacokinetics [5].

Hence; the present study was conducted for assessing the efficacy of Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease.

Materials and Methods

The present study was conducted for assessing the efficacy of Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. A total of 60 patients with confirmed diagnosis of Crohn's Disease were enrolled. Complete demographic and clinical details of all the subjects was recorded. Random division of all the patients was done into three study groups as follows:

Group 1: Azathioprine group
Group 2: Infliximab group
Group 3: Combined therapy

Oral mesalamine was continued at a stable dose. Systemic corticosteroids could be initiated with the dose maintained, increased, or decreased until week 14. Corticosteroid-free clinical remission was defined as clinical remission in patients who had not received budesonide at a daily dose of more than 6 mg or systemic corticosteroids for at least 3 weeks. The primary efficacy end point was the rate of corticosteroid-free clinical remission at week 26; the rates of corticosteroid-free clinical remission at other time points were secondary efficacy end points. All the results were recorded in Microsoft excel sheet and were analysed by SPSS software.

Results

Mean age of the patients of the Azathioprine group, Infliximab group and combined therapy group was 43.2 years, 40.7 years and 41.6 years respectively. Major proportion of the subjects of all the study groups were males. Patients with corticosteroid free clinical remission was similar in all the three groups. Patients who received systemic corticosteroids during therapy was also similar in all the three groups. Nausea, vomiting, abdominal pain, worsening of disease, fatigue, headache and arthralgia were the commonly encountered adverse events.

Table 1: Demographic data

Variable	Azathioprine group	Infliximab group	Combined therapy
Mean age (years)	43.2	40.7	41.6
Males (%)	60	65	60
Females (%)	40	35	40
Mean C reactive protein (mg/dL)	1.3	1.1	1.3

Table 2: Corticosteroid therapy

Variable		Azathioprine group	Infliximab group	Combined therapy
Patients with corticosteroid free clinical remission (%)	6 weeks	10	30	35
	10 weeks	25	35	45
	18 weeks	25	40	55
	26 weeks	30	45	60
Patients who received systemic corticosteroids during therapy (%)	6 weeks	35	50	50
	10 weeks	45	50	50
	18 weeks	55	55	50
	26 weeks	60	65	55

Table 3: Mucosal healing

Mucosal healing	Azathioprine group	Infliximab group	Combined therapy
Baseline lesions (n)	116	102	111
Final count of lesions (n)	19	29	43

Table 4: Adverse events

Adverse events	Azathioprine group	Infliximab group	Combined therapy
Nausea (%)	35	20	20
Vomiting (%)	20	20	10
Abdominal pain (%)	20	10	15
Worsening of disease (%)	20	10	15
Fatigue (%)	5	5	10
Pyrexia (%)	10	10	5
Headache (%)	10	5	10
Arthralgia (%)	10	5	10

Discussion

Crohn disease can affect any part of the gastrointestinal tract. About one-third of patients have small bowel involvement, especially the terminal ileum, another 20% have only colon involvement and about 50% have involvement of both the colon and small bowel. There is no cure and most patients experience bouts of remissions and relapse at unpredictable times. This disease leads to very poor quality of life [6- 8].

Crohn's disease affects the mouth, anus, and the entire layers of the intestine. Ulcerative colitis affects the mucosal layer of the colon. The lesions occur in the rectum and the intestine. The symptoms are mild to severe and may threaten life. The symptoms of CD and Ulcerative colitis (UC) are very similar. Malnutrition is very common in CD because the small intestine is responsible for the absorption of nutrients, and CD damages the small intestine. Ulcerative colitis is associated with blood in stool, severe pain, and

diarrhea, while in CD there is also a risk of bleeding in severe cases. Rectal bleeding is less common in CD, while UC is commonly associated with rectal bleeding. More than 50% of people with CD suffer from folate and vitamin D deficiency, while more than 50% of people with UC suffer from iron deficiency [7-9]. In addition, systemic corticosteroids and budesonide are not effective for maintenance therapy. Azathioprine and 6-mercaptopurine are frequently prescribed for patients in whom first-line therapies fail — in particular, those who are dependent on or do not have a response to systemic corticosteroids [10]. Hence; the present study was conducted for assessing the efficacy of Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease.

Mean age of the patients of the Azathioprine group, Infliximab group and combined therapy group was 43.2 years, 40.7 years and 41.6 years respectively. Major proportion of the subjects of all the study groups were males. Patients with corticosteroid free clinical remission was similar in all the three groups. Patients who received systemic corticosteroids during therapy was also similar in all the three groups. Nausea, vomiting, abdominal pain, worsening of disease, fatigue, headache and arthralgia were the commonly encountered adverse events. Our results were in concordance with the results obtained by previous authors who also reported similar findings. In a previous study conducted by Colombes JF *et al*. authors comparatively evaluated the efficacy and safety of infliximab and azathioprine therapy alone or in combination for Crohn's disease. They observed that of the 169 patients receiving combination therapy, 96 (56.8%) were in corticosteroid-free clinical remission at week 26 (the primary end point), as compared with 75 of 169 patients (44.4%) receiving infliximab alone (P=0.02) and 51 of 170 patients (30.0%) receiving azathioprine alone (P<0.001 for the comparison with combination therapy and P=0.006 for the comparison with infliximab). They concluded that patients with moderate-to-severe Crohn's disease who were treated with infliximab plus azathioprine or infliximab monotherapy were more likely to have a corticosteroid-free clinical remission than those receiving azathioprine monotherapy.[11]

In a similar study conducted in 2019 by Colombel JF *et al*, authors analysed data from 206 patients from whom week 30 serum samples were available: 97 received infliximab monotherapy (5 mg/kg, n = 97) and 109 received combination therapy (2.5 mg/kg/day; n = 109). They also concluded that among patients with CD and similar serum concentrations of infliximab, combination therapy with azathioprine was not significantly more effective than infliximab monotherapy. Combination therapy with azathioprine appears to improve efficacy by increasing pharmacokinetic features of infliximab [5].

Borrelli O *et al*. in a similar study, assessed the efficacy of infliximab in children and adolescents with severe Crohn's disease recruited consecutively and followed up prospectively at a single centre. They concluded that in children with severe Crohn's disease, infliximab is a safe and valuable treatment in inducing remission, in healing inflammatory lesions of the gut, as documented by endoscopy and histology, and in promoting growth. Retreatment infusions of infliximab may be suggested in childhood-onset Crohn's disease to maintain remission and reverse growth failure [12].

Conclusion

Under the light of above obtained results, the authors conclude that in Crohn's disease patients, infliximab monotherapy and combination therapy with infliximab plus azathioprine, in comparison to azathioprine alone, causes enhanced rates of corticosteroid-free clinical remission.

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