Original Research Article

Relative effectiveness of aminosalicylates in the management of acute ulcerative colitis - Mesalamine vs Sulfasalazine

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Abstract

Introduction: Inflammatory bowel disease (IBD) is not a single condition. It is the term for a group of disorders that cause prolonged inflammation of the digestive tract. The most common types of inflammatory bowel disease (IBD) are ulcerative colitis and Crohn's disease.

Aim: The study was designed to compare the efficacy, safety, incidence of ADR'S in patients of inflammatory bowel disease with regard to the use of mesalamine, sulfasalazine and using combination of mesalamine and steroids.

Materials and methods: This observational, non interventional study conducted in General Medicine Department and Gastroenterology department, Princess Esra hospital, shahali banda, within 6 months of duration. Patients selected randomly according to inclusion and exclusion criteria. A 110 patients aged 18 to 90 years, and presenting with complaints of abdomen pain, diarrhoea, bloody diarrhoea, painful defecation, altered appetite, bleeding per rectum were screened for the study after taking their informed consent. Patients were categorized into 4 groups; group I (control), group II (Mesalamine), group III (sulfasalazine), and group IV (Mesalamine + steroids)

Results: Patients with age group from 18-80yrs were included in the study. The age group of 31-50age was found more prone to disease. The total percentage of male and female in 110 patients was found to be 40% (male) and 60% (female). Patients with percentage of 60% male and 40% female underwent treatment with mesalamine (Group-I), 36.6%male and 63.3%female with mesalamine + steroids (Group-II), and 30% male and 70% female with sulfasalazine (Group-III) respectively. The

most common symptom was abdomen pain present in 74% patients and rectal bleeding was the next common symptom (67.21%) and other symptoms include vomiting (55.2%), loose stools (52.3%), painful defecation (44%), and reduced appetite (43.3%). The adverse effects observed during sulfasalazine treatment was abdominal pain (50%), nausea (35%), dizziness (21.6%), anorexia (16.6%), rashes (10%), gastric distress (10%), sleeping disorders (3.30%), cyanosis (3.3), hemolytic anaemia (1.60%) and mesalamine treatment was abdominal pain 21.08%, nausea 3.50%, heartburn 22%, bloated stomach 7.7% and weakness 6.64% and with mesalamine + steroids was abdomen pain 48.3%, rectal bleeding 33.3%, painful defecation 18.3%, loose tools 45%, vomiting 50% and reduced appetite 28.3%. The percentage recovery of symptoms with sulfasalazine was 60% abdomen pain, 30% rectal bleeding, 15% painful defecation, 44% loose stools, 65% vomiting, and 0% reduced appetite, with mesalamine was 40% abdomen pain, 20% rectal bleeding, 0% painful defecation, 15% loose stools, 0% vomiting, 10% reduced appetite and mesalamine + steroids was 21.6% abdomen pain, 13.3 rectal bleeding, 8.3% painful defecation, 26.6% loose stools, 15% vomiting, 18.3% reduced appetite.

Conclusion: Patients of acute IBD- acute ulcerative colitis of mild type respond faster to mesalamine with or without steroids compared to sulfasalazine alone although both drugs showed good response.

Key words

Inflammatory bowel disease, Mesalamine, Sulfasalazine steroids.

Introduction

Inflammatory bowel disease (IBD) is not a single condition. It is the term for a group of disorders that cause prolonged inflammation of the digestive tract. The digestive tract is composed of the mouth, esophagus, stomach, small intestine, and large intestine. It is responsible for breaking down food, extracting the nutrients, and removing any unusable material and waste products. Inflammation anywhere along the digestive tract disrupts this normal process. This can be very painful. In some cases, IBD can even be life threatening [1]. A group of chronic intestinal diseases characterized by inflammation of the bowel the large or s mall intestine. The most common types of inflammatory bowel disease (IBD) are ulcerative colitis and Crohn disease.

Crohn disease favors the ileum (the lower part of the small intestine) but can occur anywhere along the intestinal tract while, by contrast, ulcerative colitis affects the colon (the large intestine) alone.

The inflammation in Crohn disease involves the entire thickness of the bowel wall, whereas in ulcerative colitis the inflammation is confined to the mucosa (the inner lining) of the intestine.

Intestinal ulcers and bleeding are common in both Crohn disease and ulcerative colitis. But complications such as intestinal strictures (narrowing), fistulas, and fissures (tears) are far more common in Crohn disease than in ulcerative colitis. Small intestinal bacterial overgrowth in Crohn disease can result from an intestinal stricture and is treated with antibiotics.

Crohn disease of the duodenum and jejunum can cause malnutrition, weight loss, and diarrhoea. In Crohn disease of the ileum, malabsorption of bile salts can cause diarrhoea and malabsorption of vitamin B12 can lead to anemia.

There is an increased risk of colon cancer in ulcerative colitis. Yearly monitoring with colonoscopies and biopsies of the colon for premalignant cells and cancer is recommended for patients after 8 to 10 years of chronic inflammation of the colon. The treatment of IBD involves the use of medicines and sometimes surgery, depending upon the type and course of the inflammatory bowel disease. Effective

therapy exists for the majority of cases. Narcotics, codeine, and anti-diarrheal medications such as Lomotil and Imodium should be avoided during severe episodes of colitis because they may induce toxic mega colon [2, 3]. The study was designed to compare the efficacy, safety, incidence of ADR'S in patients of inflammatory bowel disease with regard to the use of mesalamine, sulfasalazine and using combination of mesalamine and steroids.

Materials and methods

This observational non interventional study conducted in General Medicine Department and Gastroenterology department, Princess Esra hospital, shahali banda, within 6 months of duration.

Inclusion criteria

Patients age group of 18-50 yrs with either gender was included. Patients with no co-morbid diseases, non pregnant females, no complications of APD at the time of entry in to the study were included.

Exclusion criteria

Patients in I.C.U, critical care units and other non selected departments and pregnant females were excluded.

Patient data was collected from treatment chart or case sheet and Patient data collection form. Patient data collection form will contain patient demographic details**,** co-morbid conditions, past medical and medication history**,** Family history**,** Laboratory data including UGIE reports, colonoscopy, present medication list, **a**dverse effects of the drugs and the description including the frequency, duration and type and Pre medication**.**

A 110 patients aged 18 to 90 years, and presenting with complaints of abdomen pain, diarrhoea, bloody diarrhoea, painful defecation, altered appetite, bleeding per rectum were screened for the study after taking their informed consent. Patients with endoscopic evidence and symptomatically diagnosed patients were taken under study.

Patients were randomly categorized into 4 groups.

Group - I (C) i.e. marked as control group contain 10patients (4.7%) who received treatment of Asacol, no prokinetic drug.

Another three groups received prokinetic drug.

Group II (M) i.e. marked as mesalamine group include 20 patients (66.6%) received treatment of mesalamine at doses of pentasa-1gm, mesacol – 400 mg, and vegaz-od.

Group III (S) i.e. marked as sulfasalazine group include 20 patients (28.5%) received treatment of sulfasalazine at doses of balacol-650mg, BD daily before meals.

Group IV (M+S) i.e. marked as mesalamine + steroids group include 60 patients received treatment of mesalamine and steroids at a doses of mesalamine pentasa sachet – 2 gm, and steroids Predmet – 8 mg, Predmet - 16 mg, inj. Decadron 1cc IV BD based on severity of disease.

They were advised to avoid alcohol and smoking during the study period. Patients were advised to come for follow up during the treatment. Clinical adverse events were recorded at the end of week 1 and week 2, along with their nature, intensity, action taken and outcome. Following treatment, relief of symptoms was assessed at the end of 2 weeks.

Results

A comparative study of 110 patients was conducted with inflammatory bowel disease as determined by colonoscopy, flexible sigmoidoscopy and symptoms. Patients were enrolled in a randomized manner, consisting of a colonoscopy test from start of treatment followed by 15days treatment period during which each

patient received either Mesalamine (pentasa sachet – 2 gm, pentasa – 1 gm, mesacol - 400 mg, vegaz - od) OD or Sulfasalazine (balacol 650 mg) BD daily after meals. 110 patients were divided into 4groups.

The total percentage of male and female in 110 patients was found to be 40.9% (male) and 59.0% (female).The ratio of male: female was 9:13 (**Table - 1**).

The ratio of male: female in each group include 18-30 age -7:6.5, 31-50 age -3.5:5, 51-70 age - 2.5:3, 71-90 age - 2:3. The percentage of patient age group which is more prone to disease receiving mesalamine drug was 18-30 age group and the percentage was found to be 45% (**Table - 2**).

The percentage recovery of symptoms with sulfasalazine was 60% abdomen pain, 30% rectal bleeding, 15% painful defecation, 44% loose stools, 65% vomittings,0% reduced appetite. The percentage recovery of symptoms with mesalamine was 40% abdomen pain, 20% rectal bleeding, 0% painful defecation, 15% loose stools, 0% vomiting, 10% reduced appetite. The percentage recovery of symptoms with mesalamine+steroids was 21.6% abdomen pain, 13.3 rectal bleeding, 8.3% painful defecation, 26.6% loose stools, 15% vomiting, 18.3% reduced appetite (**Table – 3, Figure – 1, 2**).

Table - 1: Gender distribution among groups.

Variable	Gender distribution		No of patients
	Male	**Female**	
Total	44 (40%)	66 (60%)	110
Group I	4(40%)	6(60%)	10
Group II	12(60%)	8(40%)	20
Group III	6(30%)	14(70%)	20
Group IV	22(36.6%)	38(63%)	60

Table - 2: Age distribution among groups.

Variable	Age distribution in years			
	18-30	**31-50**	**51-70**	**71-90**
Group I	3	7	-	-
Group II	9	10	1	-
Group III	9	8	3	-
Group IV	27	17	11	5

Improvement in ulcerative colitis and crohn's disease grades from baseline to endline was observed in 85.6% of patients in mesalamine group in comparison to 54.5% in sulfasalazine group.

Hence at the end of therapy, decrease in the number of symptoms were significantly higher in the group of patients receiving mesalamine (85.6%) with less adverse effects.

Healing rate during and at the end of treatment was better with mesalamine.

Discussion

Study was designed to compare mesalamine and sulfasalazine at standard recommended doses as healing and prophylactic treatment for patients having inflammatory bowel disease.

Table - 3: Distribution of symptoms among groups before, during and after treatment.

Distribution of symptoms among groups before treatment				
Symptoms	**Control**	**Sulfasalazine**	**Mesalamine**	**Mesalamine + Steroids**
Abdomen pain	70%	75%	85%	58.3%
Rectal bleeding	80%	60%	40%	48.3%
Painful defecation	40%	40%	30%	33.4%
Loose stools	60%	85%	40%	75%
Vomiting	80%	40%	60%	80%
Reduced appetite	50%	25%	35%	46.6%
Distribution of symptoms among groups during treatment				
Abdomen pain	70%	45%	55%	48.3%
Rectal bleeding	50%	40%	20%	33.3%
Painful defecation	0%	35%	0%	18.3%
Loose stools	20%	55%	15%	45%
Vomiting	30%	40%	20%	50%
Reduced appetite	10%	25%	0%	28.3%
Distribution of symptoms among groups at end of treatment				
Abdomen pain	30%	60%	40%	21.6%
Rectal bleeding	70%	30%	20%	13.3%
Painful defecation	0%	15%	0%	8.3%
Loose stools	70%	65%	15%	2.66%
Vomiting	45%	20%	0%	15%
Reduced appetite	30%	0%	10%	18.3%

Figure - 1: Bar diagrams showing adverse effect before treatment.

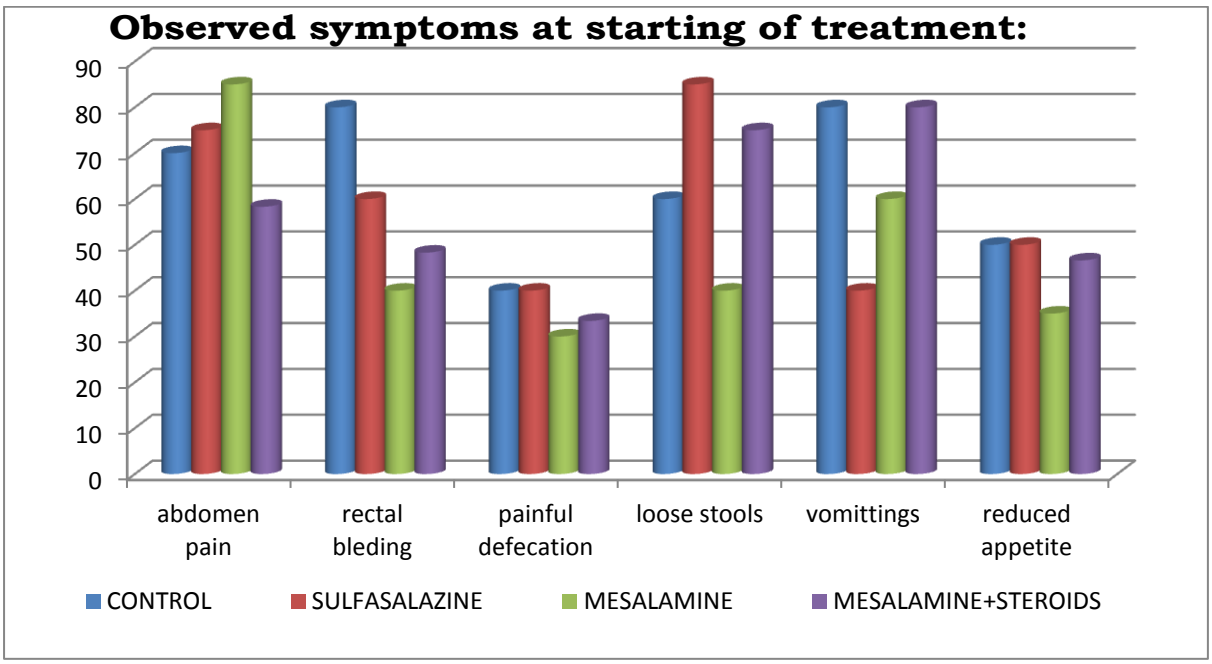
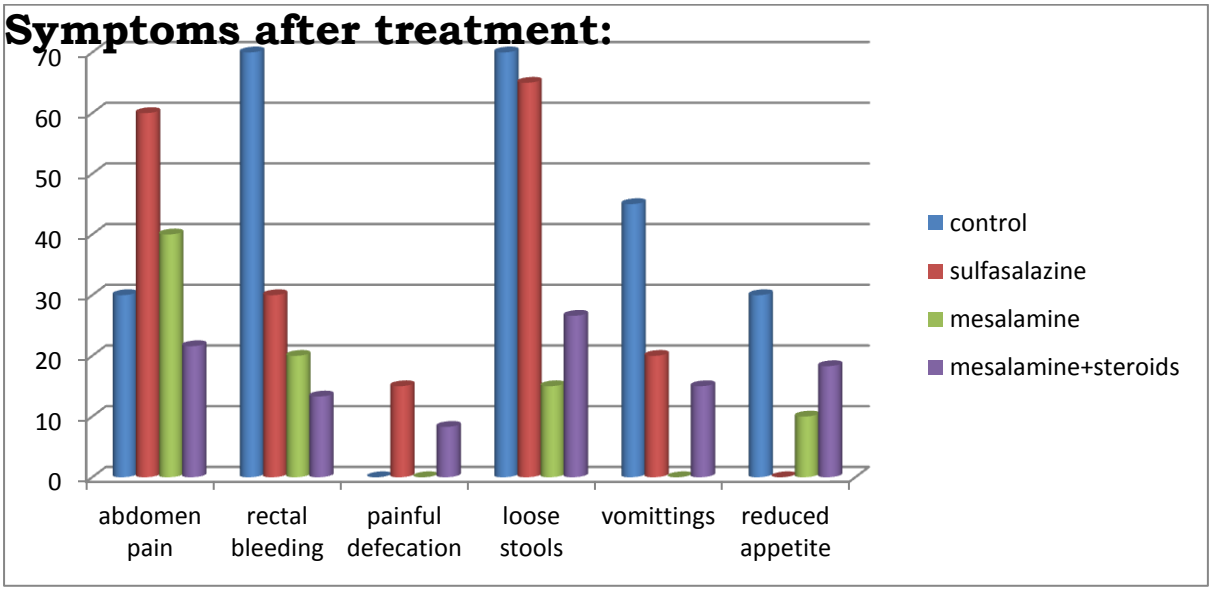


Figure - 2: Bar diagrams showing adverse after before treatment.



Patients with percentage of 60% male and 40% female underwent treatment with mesalamine (Group-I), 36.6%male and 63.3%female with mesalamine + steroids (group-II), and 30% male and 70% female with sulfasalazine (Group-III) respectively.

Patients with age group from 18-80 years were included in the study. The age group of 31-50 age was found more prone to disease.

In both the groups, the age group of 18-30 have high percentage of patients with complains.

The symptoms before treatment in control and test groups showed high incidence of diarrhea followed by abdomen pain, rectal bleeding, painful defecation, reduced appetite.

Improvement in symptoms was observed during the treatment in 85.6% mesalamine taking (Group-I) and 54.5% in sulfasalazine taking (Group-III) patients.

More than 50% of patients show a significantly positive effect on symptoms was described after 15 days with pentasa 2 gm OD after meals, pentasa 1gm, mesacol-400, vegaz-od BD after meals.

In severe active phase of the disease mesalamine along with steroids (Group-II) was used in high doses and on remission the dose was reduced, and then the treatment was followed with only mesalamine.

The treatment of IBD requires a long term therapy as the recurrence of disease is very high.

Due to long term therapy there is a high risk of developing of ADR'S with both mesalamine and sulfasalazine, which should be treated simultaneously.

As steroids is also used in the treatment there is increase risk of ADR'S from steroids also, which should be treated simultaneously. Following the treatment, symptoms recovery was good with both the drugs but more was seen with mesalamine. During the treatment, adverse effects has been observed in both the groups, the common adverse effects are abdominal pain, nausea, heart burn and skin rashes.

Adverse effects has reverts to normal after specific treatment. Complain of vomiting, nausea, heartburn was observed more with sulfasalazine during and after treatment than mesalamine.

Hence mesalamine appears a better drug. Improvement in Inflammatory bowel disease grades from baseline to endline was observed in 85.6% of patients in mesalamine in comparison to 54.5% in sulfasalazine patients. Hence, at the end of therapy, decrease in the number of symptoms was significantly higher in group of patients receiving mesalamine with less adverse effects.

After 15 days of therapy, the symptoms score of patients treated with mesalamine was positively influenced in contrast to the sulfasalazine treated group.

Mesalamine had significantly better symptomatic relief when compared with sulfasalazine.

Overall analysis revealed that Mesalamine was superior to Sulfasalazine with the greatest symptom score improvement. The quality of life of the treated individuals, evaluated at the end of the study was also better than sulfasalazine group. According to these results, there is no doubt that Mesalamine therapy positively influences the symptoms. The rate of treatment success with mesalamine is more than sulfasalazine.

Crohns disease is a chronic relapsing disease characterized by periods of apparent remission and obvious disease activity. Munkholm P, langholz E, Davidsen M, et al. in a Population based data from Denmark have demonstrated that within a year of diagnosis more than 50% of patients are in remission, about one third have highly active disease, and 15% have only mild disease [4].

Silverstein MD, loftus EV, sandborn WJ, et al. A Markov model of a population-based inception cohort from Olmsted country, Minnesota, suggested a patient with crohns disease would spend 24% of the time in medical remission on no medical therapy, 27% of the time being treated with mesalamine only, 41% of the time in postoperative remission, and only 7% of the time in a state requiring therapy with corticosteroids or immunosuppressants [5].

Hanauer SB, Feagan BG, Ghosh S, in a study found that The standard therapies available to clinician includes 5-aminosalicylates, sulfasalazine, antimicrobial therapy, corticosteroids, immunosuppressive agents, and monoclonal antibodies.Therapy for crohns disease should be thought of as induction therapy, followed by maintenance therapy [6].

Summers RW, Switz DM, Malchow H, Singleton JW, in a study showed that the Induction therapy for patients with mild-to-moderate crohn's disease has traditionally consisted of 5-aminosalicylates or sulfasalazine along with antimicrobials agents such as ciprofloxacin and metronidazole [7]. Faubion WA jr, Loftus EV jr, Harmsen WS in a population based study found that Induction therapy with corticosteroids, however, is highly effective strategy. Population-based studies demonstrate that after 30 days prednisone results in remission in 48%-58% of patients, response in 26%-32%, and lack of response in 16%-20%. Similar results were observed in a comparable cohort from the United Kingdom. However, prolonged response occurs in only 32%-44% and corticosteroids dependence occurs in 28%-36% [8].

Kane SV, Schoenfeld P, Otley A, Thomsen OO Rutgeerts P, Lofberg R in a styudy found For patients who have mild-to-moderate crohns disease that is limited to the ileum and right colon, controlled-release oral budesonide is a good option at a dose of 9mg/d, which has been shown to be more effective then placebo or mesalamine at inducing response and remission and causes fewer corticosteroids side effects than systemic Glucocorticoids [9]. Vermiere S, khaliq-kareemi M, Lawrence IC, et al. in a study found Many clinicians still commonly apply a stepwise approach to the management of mild crohn's disease, using induction therapy with agents with limited toxicity (e.g.; antimicrobials, mesalamine or budesonide for ileal-right colonic disease) followed by maintenance therapy with

an immunosuppressive agent after 1 or 2 episodes of symptomatic relapse, particularly in patients who lack obvious clinical predictors of severe disease [10].

In patients with moderate-to-severe crohns disease, most clinicians would use systemic corticosteroids for induction therapy with the addition of an immunosuppressive agent concomitant with induction corticosteroids or after one symptomatic relapse. In recent years, the use of immunosuppressive therapy has increased significantly. Biologic agents have traditionally been used only after the failure of or intolerance to immunosuppressive therapy. In general, this escalating approach is referred to as "step-up therapy".

Lichtenstein GR Kamm MA, Boddu P, in 2007 in a study found that the Induction therapy of mil-to-moderate ulcerative colitis generally consists of 5-aminosalicylate therapy (sulfasalazine or mesalamine), which, unlike crohns disease, is highly effective strategy. Approximately 40%-80% of patient will respond within 4 weeks to orally administered 5-aminosalicylates [11]. Safdi M, deMicco M, Gassull M, et al. The optimal approach to therapy, regardless of the extent of the disease, is combined oral and rectal aminosalicylates. For those patients who do not initially respond to 5-aminosalicylates or who have more severe symptoms, corticosteroids are an effective induction therapy [12].

Faubion WA jr, Loftus EV jr, Harmsen WS from Olmsted country, Minnesota have demonstrated that at 30 days, 54% of patient achieve complete remission, 30% achieve partial remission, and 16% fail to respond. At one year, 49% maintain response, 22% are corticosteroid dependent, and 29% go on to require colectomy. Therefore, the requirement for a course of corticosteroids in ulcerative colitis can also be seen as a bad prognostic indicator [13].

Data should be examined with respect to the ability of the available therapeutic agents in terms of inducing mucosal healing, as this is likely to be better reflective of their true efficacy.

In IBD, mucosal healing data are available for corticosteroids, methotrexate, and infliximab. Mucosal healing data for corticosteroids are limited. In crohns disease and ulcerative colitis, the use of corticosteroids has not been associated with si gnificant degrees of mucosal healing [14].

Until recently, there were limited data regarding mucosal healing with the use of mesalamine in ulcerative colitis. However, with the recent development of multi-matrix system (MMX) mesalamine, there are mucosal healing data from trials in ulcerative colitis. At 8 weeks, approximately 35% to 40% of patients on 2.4 to 4.8 g/d of MMX mesalamine achieved mucosal healing in 2 pivotal trials of this agent. There are no mucosal healing data for mesalamine in crohns disease.

To date, there has been no association between the 5-aminosalicylates class of medications and lymphoma in IBD. 5-ASA is a major metabolite of salicylazosulfapyridine. In rodent models and in vitro studies, SASP,5-ASA, and sulfapyridine have not been demonstrated to exhibit mutagenicity or DNA reactivity, nor were they found to be genotoxic [15]. Corticosteroids, specifically oral prednisone, have been mainstay in the therapy for IBD. Despite having numerous well-known side effects, corticosteroids have not been associated with an increased risk of lymphoma. In addition, because of the widespread immunosuppressant effects of corticosteroids, combination therapy, with other immunosuppressive medication could theoretically potentiate the risk of immunosuppression-related lymphoma [16].

According to Zain Kassam,, Sara Belga, Idan Roifman, Simon Hirota, Humberto Jijon, Gilaad G. Kaplan, Subrata Ghosh, and Paul L. Beck have found CD and UC have slightly different causes of mortality; however, malignancy and colorectal cancer–associated mortality remains controversial in IBD. CD mortality seems to be

driven by gastrointestinal disease, infection, and respiratory diseases. UC mortality was primarily attributable to gastrointestinal disease and infection. *Clostridium difficile* infection is an emerging cause of mortality in IBD. UC and CD patients have a marked increase in risk of thromboembolic disease. With advances in medical and surgical interventions, the exploration of treatment-associated mortality must continue to be evaluated [17].

According to Maggie Ham and Alan C Moss Ulcerative colitis (UC) is a chronic disease of the GI tract that is characterized by mucosal inflammation in the colon. Mesalamine (mesalazine) is a 5-aminosalicylic acid compound that is the first-line treatment for patients with mild-to-moderate UC. There are multiple formulations of mesalamine available, primarily differentiated by their means of delivering active mesalamine to the colon.

Mesalamine has been demonstrated in randomized controlled trials to induce both clinical response and remission, and maintain clinical remission, in these patients. It has few serious adverse effects and is generally well tolerated by patients. The main areas of uncertainty with use of mesalamine in patients with UC center on the optimal dose for induction of response, how to maintain patient adherence and the role of mesalamine in cancer chemoprophylaxis. Generic forms of mesalamine have yet to be approved by regulatory bodies in the USA [18].

According to I. M. Nakshabendi, A. Duncan, and R. I. Russell To compare the efficacy of Asacol (mesalazine coated with Eudraget-S) as a maintenance therapy with that of sulphasalazine, relapse rates of patients with ulcerative colitis and Crohn's disease, treated with sulphasalazine or Asacol were assessed in a retrospective study. A total of 164 patients were investigated, 127 on sulphasalazine and 37 on Asacol [19].

None of the patients on Asacol was changed from sulphasalazine because of lack of efficacy to sulphasalazine. Relapse rates were measured over a 4 year period. In ulcerative colitis these were sulphasalazine 10/77 (13.0%), Asacol 5/20 (25.0%), NS; in all Crohn's disease patients, sulphasalazine 12/50 (24.0%), Asacol 11/17 (64.7%); P less than 0.0025. In patients with Crohn's disease with ileal involvement, relapse rates were sulphasalazine 9/28 (32.1%), Asacol 9/11 (81.6%) and P value is less than 0.0125; without ileal involvement, sulphasalazine 3/22 (13.6%), Asacol 2/6 (33.4%), NS. This study suggests that Asacol is as effective as sulphasalazine in maintaining remission in ulcerative colitis and in patients with Crohn's disease without ileal involvement. Sulphasalazine seems to be more effective than Asacol in maintaining remission in patients with Crohn's disease with terminal ileal involvement [20].

According to Ardizzone S, Petrillo M, Imbesi V, Cerutti R, Bollani S, Bianchi Porro G, 112 patients (66 male, 46 female, mean age 35 years), with intermittent chronic ulcerative colitis in clinical, endoscopic and histological remission with sulphasalazine or mesalazine for at least 1 year, were included in the study. Assuming that a lower duration of remission might be associated with a higher relapse rate, the patients were stratified according to the length of their disease remission, prior to randomization into Group A (Asacol 26, placebo 35) in remission from 1 to 2 years, or Group B (Asacol 28, placebo 23) in remission for over 2 years, median 4 years. Patients were treated daily with oral Asacol 1.2 g vs. placebo, for a follow-up period of 1 year.

In Group A, whilst no difference was found between the two treatments after 6 months, mesalazine was significantly more effective than placebo in preventing relapse at 12 months [Asacol 6/26 (23%), placebo 17/35 (49%), P = 0.035, 95% Cl: 48-2.3%]. In contrast, in Group B no statistically significant difference was observed between the two treatments, either at 6 or 12 months [Asacol 5/28 (18%), placebo 6/23 (26%), P = 0.35, 95% Cl: 31-14%] of follow-up. Patients in group B were older, and had the

disease and remission duration for longer, than those in Group A [21].

First line therapy of inflammatory bowel disease

According to Poullenot F, Laharie D During the last decade, anti-TNF agents and emergence of new therapeutic concepts have dramatically changed inflammatory bowel disease (IBD) management, especially at their early phase. Salicylates remain the therapeutic basis in ulcerative colitis while their efficacy in Crohn's disease has not been confirmed. A rapid step-up approach is considered for managing IBD at early phase providing early immunomodulators such as immunosuppressant and anti-TNF--in case of poor disease course. Some specific situations (severe, extended or complicated forms) require the most efficient first-line therapy that is combination between anti-TNF and immunosuppressant. A close follow-up not only based on clinical symptoms, but also on objective inflammatory tools (endoscopy, cross-sectional imaging, biomarkers), is needed to adjust medical therapy rapidly in order to prevent complications and surgery [22].

Conclusion

The incidence of ADR'S was less in mesalamine group than in sulfasalazine group. The ADR'S seen in both these groups were reverted to normal after decreasing the dose or by adding specific treatment. The quality of life in patients treated with mesalamine group was found better than sulfasalazine group. In view of longer use of these drugs in long term management of IBD, we have to look at efficacy, safety and ADR'S as mentioned above. Mesalamine appears to be a better drug than sulfasalazine in long term use.

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