

Study on Follow-Up of Ulcerative Colitis Patients on Sulfasalazine At Our Hospital – Retrospective cohort Study.

Dr.S.B.Malipatil*, Dr.R.Balamurali

Department of Digestive Health and Diseases (DDHD), Government Peripheral Hospital, Kilpauk Medical College, Chennai.

*Author: Dr. SHARANABASAVAPPA. B.M

Corresponding Author: Dr. BALAMURALI RANGACHARI

Abstract:

INTRODUCTION: Ulcerative colitis is a chronic inflammatory disease of the colon of unclear etiology with an increasing incidence in India. Typical symptoms are diarrhoea, rectal bleeding, abdominal pain and fever. Sulfasalazine is effective well tolerated first line therapy for mild, moderate and severe ulcerative colitis.

AIM: To Study the Clinical Remission in Ulcerative Colitis patients on Sulfasalazine at our hospital.

METHODS: Retrospective data of 70 Patients with Ulcerative colitis on sulfasalazine, diagnosed by Clinical, Endoscopic and Histopathologic evaluation, from year 2014-2017 at our hospital were included in the study and patients with other comorbidity, non-compliance to treatment, on azathioprine or biologicals were excluded. The primary end point was Clinical remission based on Mayo score.

RESULTS: Retrospective data from 70 patients with ulcerative colitis diagnosed at our hospital from year 2014-2017 were collected. Out of 70 patients (Male=43, female=27) with age group of 24-56 years and mean age of 40 years with average symptom duration of 6 months prior to our hospital visit. All were reassessed during follow up at our hospital and classified into Mild UC group (n=23), Moderate UC group (n=31) and Severe UC group (n=16) using Truelove and Witts classification. Mild UC patients were responded in the form reduction in stool frequency from 3-4/day with blood streak to normal stool frequency with no rectal bleeding in 6 months of treatment with sulfasalazine and no exacerbations. Among Moderate UC patients 26 responded well in the form of reduction in stool frequency from 4-5/day with obvious blood to 1-2/day with no blood in stool, with 6 month of sulfasalazine and initial steroid for 10 days, 4 lost follow up, 1 was steroid dependent. Among severe UC 9 responded well from stool frequency of >6/day with frank blood to 1-2/day with occasional blood streak in stool, with 6 months of sulfasalazine and initial steroid for 10 days, 03 were steroid dependent, three were refractory to conventional treatment with development of mild dysplasia on histopathology in 2 among 3 and 1 required emergency colectomy for Toxic mega colon. Meanwhile both moderate and severe UC patients developed recurrent exacerbations requiring steroid for duration of 10 days, reasons for exacerbation were Infections, change in environment (eg: Travel).

CONCLUSIONS: Sulfasalazine still represents effective and well-tolerated first-line therapy for mild, moderate and severe ulcerative colitis as well as for the long-term maintenance treatment in the era of Biologicals and other Immunosuppressant.

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I. Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of unknown etiology affecting the large bowel with an increasing incidence in India. It can affect any age group; however, it is more common in younger populations with a peak onset between 15 and 30 years. There is an equal incidence found in both genders with bimodal incidence commonly seen in IBD. The clinical course for patients with UC is one that follows a relapsing and remitting course, with symptoms of bloody diarrhea, rectal urgency and abdominal pain. The overall principle in the pathophysiology of ulcerative colitis is the dysregulation of the normal immune system against an antigenic trigger leading to a prolonged mucosal inflammatory response. Diffuse mucosal inflammation involves the rectum in 95% of cases, and may extend proximally, involving parts or all of the colon. In addition, patients may suffer from extraintestinal manifestations of UC, including episcleritis, scleritis, uveitis, peripheral arthropathies of small and large joints, erythema nodosum, pyoderma gangrenosum, axial arthropathies, sacroiliitis, ankylosing spondylitis and primary sclerosing cholangitis. There is an increased risk for colorectal cancer (CRC) with longstanding inflammation, with risks reported as being 0.5–1% per year. Treatment options for patients with UC involve either chronic medical therapy to suppress intestinal inflammation or a colectomy (surgical removal of the colon) to remove the diseased organ. Medical

management usually involves a ‘step-up’ approach, starting with topical or oral agents, and ascending to more complex agents, with risk of more serious adverse effects, in those who do not respond to first-line agents. The type and formulation of therapy recommended for patients with UC is dependent on both the location of the disease and the degree of severity.

Pathophysiology

The overall principle in the pathophysiology of ulcerative colitis is the dysregulation of the normal immune system against an antigenic trigger. The aggregate effect of genetic, environmental, and other processes is a sustained activation of the mucosal immune response.

A state of altered immune regulation leading to prolonged mucosal inflammatory response and thus resulting in the recruitment of leukocytes from the gut vasculature exists in UC. The mucosa in patients with UC may be dominated by CD4+ non-T helper lymphocytes generating a humoral immune profile. Defective colonic mucosa allows the access of luminal dietary and bacterial products to the mucosa. The possible antigenic triggers currently proposed include microbial pathogens, non-pathogenic microbial agents, dietary antigens and an autoimmune mechanism. Animal models using knock out genes that affect the mucosal immune system or epithelial integrity have resulted in intestinal mucosal inflammation in non-germ-free environments. This therefore supports the fact that the presence of luminal bacteria and the absence of regulatory proteins in the mucosal immune system are generally required for development of intestinal inflammation. Furthermore, an uncontrolled immune activation with failure of suppression is a commonly explained mechanism of inflammatory bowel disease. Proinflammatory mediators, or cytokines, are also known to play an important role in UC, with evidence to support increased levels of IL-1, IL-6, IL-8 and tumor necrosis factor (TNF-a).

Clinical presentation and diagnosis

The most common clinical course in patients with ulcerative colitis is chronic intermittent with approximately 10% of cases presenting as acute fulminating (Powell-Tuck and Truelove 1963). Between episodes, patient may be free of symptoms. Symptoms are related to the extent of the disease, with common clinical features being intermittent rectal bleeding, tenesmus, crampy pain, passage of mucous, and mild diarrhea. When the disease is severe, more systemic features can be seen. These include fevers, weight loss, severe abdominal pain, anemia, and malnutrition. Based on clinical and endoscopic findings the disease is characterized as to its severity and extent (Kornbluth and Sachar 2004). This allows clinicians to predict the extent of involvement and better assess the level of acuity of the patient. The most severe complication from an UC flare is toxic megacolon, which often requires surgery. If the disease is confined to the rectum, the patient may only complain of urgency and primarily tenesmus with bloody bowel movements and diarrhea.

Anatomic distribution of disease by endoscopic evaluation can be used to describe the degree of involvement and the state of activity. Almost all cases of UC have rectal involvement. Ulcerative proctitis is a disease limited to the rectum, whereas proctosigmoiditis extends to the mid sigmoid colon, left sided colitis extends to splenic flexure (30%) and extensive colitis extends beyond splenic flexure but not reaching cecum (20%) and pancolitis extends all the way to cecum. The various states of activity can be described as relapsing, mild/moderate active, severe active and remission, while the degree of severity of UC is described as mild, moderate, and severe and distinguished by frequency of bowel movements, abdominal symptoms, extent of colonic involvement, presence of fever or bleeding per rectum (Table 1). Mild is defined as less than 4 bowel movements a day, normal ESR and no signs of systemic toxicity and fulminant is defined as greater than 10 bowel movements a day, continuous bleeding, systemic toxicity, abdominal tenderness, transfusion requirement, and colonic dilation on x-ray. Therefore, once the diagnosis can be confirmed and the degree of involvement and activity can be determined, the specific treatment regimen is initiated. The diagnosis of UC is made by combining the clinical picture with the endoscopic appearance of mucosal ulceration, friable, edematous, erythematous granular appearing mucosa, often described as “sand sprinkled on a moist surface”(Table02).Biopsy results suggestive of UC include crypt abscesses, superficial microulcerations, and inflammatory infiltrate. Other histological findings include widespread crypt distortion and loss, and marked goblet cell mucin depletion. With chronic inflammation the architecture of the crypts are distorted, becoming branched, shortened and atrophied. One must remember that the clinical presentation and endoscopic findings are non specific and infectious and other acute self limiting causes of colitis must always be excluded.

Table -01: True Love And Witts Criteria For Severity Of Uc

Mild
<4 stools/day, without or with only small amounts of blood No fever

No tachycardia Mild anemia ESR < 30 mm/hr
Moderate
Intermediate between mild and severe
Severe
>6 stools/day, with blood Fever > 37.5°C Heart rate > 90/min Anemia with Hgb level <75% of normal ESR > 30 mm/hr

Table -02 Mayo Score for the Severity of UC

Score Criteria	
Stool Frequency	
0	Normal
1	1-2 stools/day more than normal
2	3-4 stools/day more than normal
3	5 or more stools/day more than normal
Rectal Bleeding	
0	None
1	Streaks of blood with stool less than half the time
2	Obvious blood with stool most of the time
3	Blood alone passed
Mucosal Appearance	
0	Normal
1	Mild disease (erythema, decreased vascular pattern, mild friability)
2	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	Severe disease (spontaneous bleeding, ulceration)
Physician Global Assessment	
0	Normal
1	Mild disease
2	Moderate disease
3	Severe disease

Treatment of ulcerative colitis

Introduction

The approach to therapy of UC has been dependent on severity of symptoms with frontline therapy being aminosalicylates. The intolerance of sulfasalazine being a restrictive factor, newer formulations have been developed which are free of the sulphur component and have better side-effect profile. These drugs are composed of 5-ASA, the active moiety of sulfasalazine, without the sulfapyridine carrier molecule that is usually the main cause of the side effects. Mesalamine is one of the 5-ASA based agents currently available and indicated for treatment of UC. This review will examine the evidence for 5-ASAs in the treatment of ulcerative colitis. The different 5-ASA formulations will be discussed and compared and the current data available regarding efficacy, dosages and side effect profile will be presented.

Sulfasalazine

Sulfasalazine aminosalicylate in use for over 60 years (Hanauer 2004) and consists of 5-aminosalicylic acid linked by an azo bond to sulfapyridine. It combines an antibacterial agent (sulfapyridine) with an anti-inflammatory component (5-ASA). The sulfonamide moiety acts as a carrier to deliver the active component 5-ASA to the colon where it is released by bacterial action. Sulfasalazine is metabolized by colonic bacterial enzymes to produce the two active byproducts. Sulfapyridine is metabolized by the liver and excreted in the urine whereas the 5-ASA component is acetylated by the colonic epithelium. The original indication for 5-ASA was for rheumatoid arthritis, however it was subsequently found to be efficacious in ulcerative colitis. Misiewicz et al (1965) published the first placebo controlled maintenance trial in 1965 randomizing patients to receive sulfasalazine or placebo for one year. Seventy three percent of patients taking placebo relapsed compared to 21% taking the active drug, thus showing sulfasalazine to be highly efficacious for the treatment of ulcerative colitis. Due to the intolerance of sulfasalazine being a restrictive factor in optimizing the therapeutic dosage, more tolerable mesalamine-based drugs have been developed void of the sulphur component. These new formulations are composed of 5-ASA, the active moiety of sulfasalazine, without the poorly tolerated sulfapyridine carrier molecule. The newer generation aminosalicylates allow for targeted delivery with reduced side effects observed with sulfasalazine. These new formulations also allow for earlier release more proximally in the small intestine. An added benefit also includes variability in the pH dependent site of release of various aminosalicylates. A variety of different mechanisms have been proposed by which aminosalicylates work in inflammatory bowel disease. The main mechanism includes the inhibition of cyclooxygenase and lipoxygenase pathways to reduce the production of prostaglandins and leukotrienes, respectively. Mesalamine also reverses the antiproliferative effects of TNF-alpha thus disrupting the effect of cytokines by reducing intestinal cell transcription of inflammatory mediators Other processes described include inhibition of platelet activating factor and production of oxygen radicals and other anti-inflammatory factors By reducing inflammatory prostaglandin production and the formation of other potent chemotactic substances including leukotriene B4 and certain hydroxy fatty acids, mesalamine plays a significant role in halting the perpetuation of a chronic inflammatory state.

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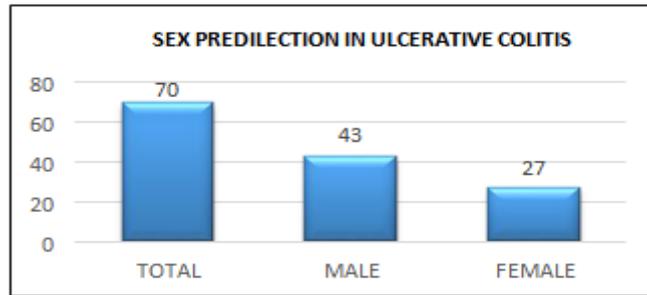
II. Results

Out of 70 patients (Male=43, female=27) with age group of 24-56 years and mean age of 40 years with average symptom duration of 6 months prior to our hospital visit were reassessed during follow up at our hospital for a period of 3 years and classified into Mild UC group (n=23), Moderate UC group (n=31) and Severe UC group (n=16) using Truelove and Witts classification.

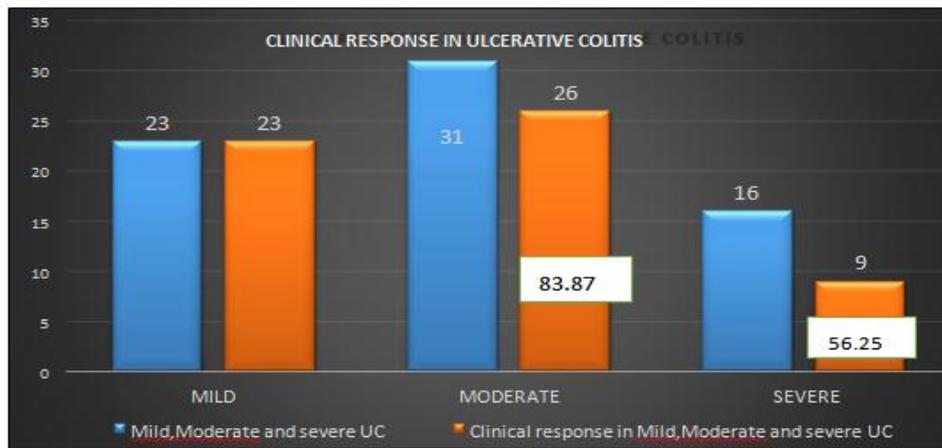
- 1) Mild UC patients were responded in the form reduction in stool frequency from 3-4/day with blood streak to normal stool frequency with no rectal bleeding in 6 months of treatment with sulfasalazine and no exacerbations.
- 2) Among Moderate UC patients 26 responded well in the form of reduction in stool frequency from 4-5/day with obvious blood to 1-2/day with no blood in stool, with 6 month of sulfasalazine and initial steroid for 10 days, 4 lost follow up, 1 was steroid dependent.
- 3) Among severe UC 9 responded well from stool frequency of >6/day with frank blood to 1-2/day with occasional blood streak in stool, with 6 months of sulfasalazine and initial steroid for 10 days, three were steroid dependent, three were refractory to conventional treatment with development of mild dysplasia on histopathology in 2 among 3 and 1 required emergency colectomy for Toxic mega colon. Meanwhile both moderate and severe UC patients developed recurrent exacerbations requiring steroid for duration of 10 days, reasons for exacerbation were Infections, change in environment (eg: Travel).

All results are shown in following diagram.

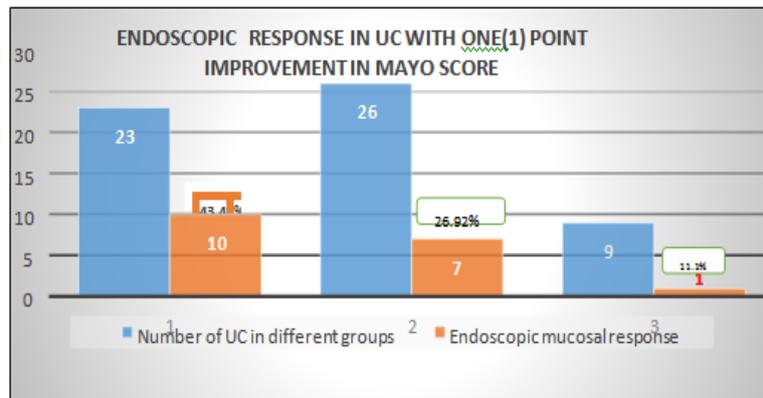
A) Sex predilection in UC(M>F)



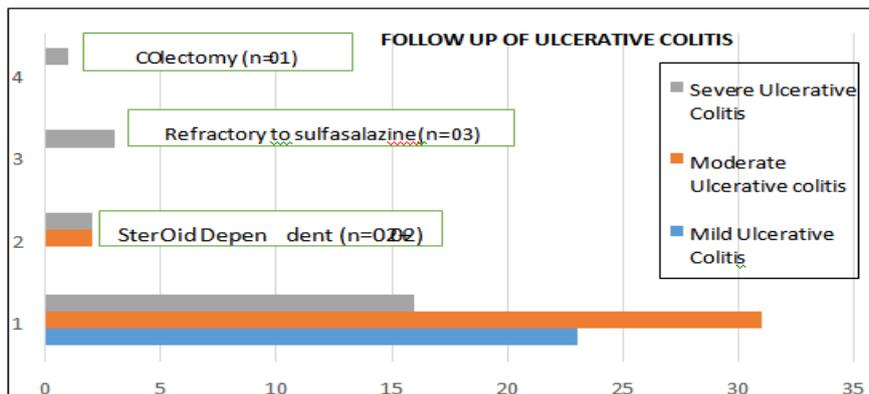
B) Clinical response in UC on Sulfasalazine



C) Endoscopic response in UC on Sulfasalazine



D) Follow up of UC on sulfasalazine:



III. Conclusions

Although there is no evidence of greater clinical response of mesalamine versus other 5-ASA preparations, there is adequate data to support the effectiveness of sulfasalazine in mild/moderate active disease with response rates between 40%–70% and remission rates of 15%–20% (Sninsky et al 1991; Kornbluth and Sachar 2004; Hanauer et al 2005). However, in studies comparing mesalamine, there was no increased effectiveness of 5-ASA over sulfasalazine (Sutherland and MacDonald 2006). Two studies have shown that delayed – release of sulfasalazine showed significant benefit compared with placebo (Schroeder et al 1987; Sninsky et al 1991). It was demonstrated that sulfasalazine 3–4 g/d had a higher complete response compared to those taking placebo (24% vs 5% $p = 0.047$) as well as higher partial response (50% vs 13%, p value not given) (Kane and Bjorkman 2003). The clinical response was based on predetermined criteria that included stool frequency, rectal bleeding, sigmoidoscopic appearance of the mucosa. A complete response was defined as total resolutions of all symptoms, whereas a partial response was a substantial but incomplete improvement in clinical parameters. Aminosalicylate therapy remains the foundation for treating colitis and maintaining remission in mild to moderate ulcerative colitis. Over the years new formulations have been developed to make this product more tolerable and efficacious. Mesalamine a 5-ASA is the active moiety of the precursor drug sulfasalazine, is significantly more tolerable than its predecessor. Considering that the efficacy of 5-ASA is dose dependent, 3g/day have been shown to be the optimal dosages for active disease and for maintenance therapy, in our study. As for leftsided colitis, topical (rectal) formulation is superior in inducing remission. Mesalamine is an excellent first-line therapy for a step up approach in treating mild to moderate ulcerative colitis and for maintenance of remission. Furthermore, different modes of delivery have also been developed to enhance the therapeutic efficacy of these products. Overall treatment decisions should be based on the severity and extent of disease. A factor which will influence success of therapy is maximizing mucosal concentration of therapy by localizing the area of involvement and therefore utilizing the most appropriate delivery formulation. Compliance being a restrictive factor in treatment success, new formulations have been developed which will require less frequent dosing. Considering that UC is a chronic remitting active inflammatory condition, patients will most likely need lifelong therapy.

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