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Current medical therapy of inflammatory bowel disease

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INTRODUCTION

The 1990's have brought a significant promise and the hope for a better and brighter future in the new millennium for patients with inflammatory bowel disease (IBD). A better understanding of the pathophysiology of IBD symp toms has led to newer treatment modalities and streamlining of therapy for specif ic subsets of patients.

ULCERATIVE COLITIS

The treatment for ulcerative colitis (UC) is aimed at modulating the inflammator y response. The drugs which are found to be effective are sulfasalazine (Azulfi dine, Salazopyrin) and its 5ASA derivatives, glucocortico-steroids, immunomodul ators/immunosuppressants, and other new potential drugs (Table 1).

Table 1 Medical therapy in IBD

Sulfasalazine and 5-amino salicylates	Azulfidine
	Olsalazine, Asacol, Pentasa, Balsalazide
Corticosteroids	Hydrocortisone, ACTH, Prednisone, Budesonide
Immunosuppressive / Immunomodulators	Immuran / 6MP, Cyclosporin A, Methotrexate,
	Anti-TNFα Antibody, (Remicade, CD P571)
	FK506, IL-10, IL-11
	IL-1 Receptor Antagonist, Anti-CD4 Antibody
Antibiotics	Metronidazole, Ciprofloxacin,Clarithromycin,
	Trimethoprim-sulfamethoxazole
New potential drugs	Nicotine
	Heparin
	ISIS 2302 (ICAM-1 inhibitor)
	Hydroxychloroquine, Leukotrienes inhibitors,
	Short chain fatty acids
	Antioxidants & free radical scavengers
	Probiotics

Sulfasalazine and 5-ASA compounds

Initially developed in the 1940s for the treatment of rheumatoid arthritis, sali cyl-azo-sulfapyridine, or sulfasalazine was quickly recognized as being effec a cious in the treatment of colitis. Consisting of a molecule of 5-aminosalicylic acid (5-ASA) joined by an azo bond to a molecule of sulfapyridine (Figure 1), sulfasalazine has been a mainstay in the treatment of UC for more than 50 years[1].

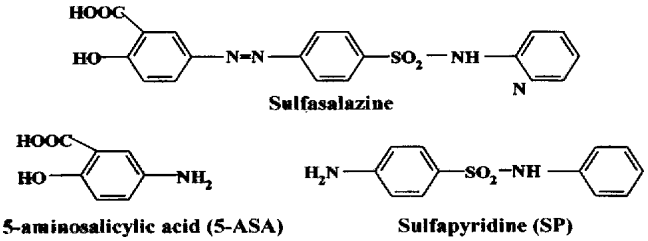

Figure 1 Structure of salicyl-azo-sulfapyridine or sulfasalazine (azulfidine , salazopyrin).

The active moiety in sulfasalazine is 5-ASA, with the sulfapyridine acting as a carrier to prevent absorption of 5-ASA in the small bowel. In the distal ileum and colon, bacteia that possess azo reductase split the molecule, releasing free 5-ASA and sulfapyridine (Figures 1,2). Almost all colonic bacteria have azore ductase enzyme. The sulfapyridine is readily absorbed from the colon, acetylate d in the liver, and conjugated with glucuronic acid, and excreted in the urine[1]. The 5-ASA is only minimally absorbed, with the majority being excreted in the feces unchanged (Figure 2). 5-ASA's mechanism of action is by direct contact with colonic mucosa to suppress various pro-inflammatory pathways including both cyclooxygen ase and lipoxygenase derived products such as prostaglandins and leukotrienes from arachidonic acid and from suppression of superoxide dismutase and possibly by other mechanisms.

Sulfasalazine has been well studied in UC and has proven efficacy in inducing remisson in patients with mild-to-moderate disease, as well as in maintaining r emission. Its use has not been studied in a controlled manner for severe UC, but it is commonly used as an adjunct to approximately 80% of patients with mild-to-moderate disease, compared with 30% to 35% of those receiving placebo. Studies examining maintenance of remission have shown that sulfasalazine's effect is d ose-dependent, with relapse rates of 33% with 1 g/day, 14% with 2 g/day, and 9 % with 4 g/day[2].

The toxic effects of sulfapyridine are the limiting factor in using sulfasalazin e. Common adverse reactions include headache, nausea, anorexia, and dyspepsia. These

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symptoms relate to plasma levels of sulfapyridine and usually occur at dosa ges greater than 3 g/day [3]. Because of sulfasalazine's substantial to xicity and the limitation of dosing due to side effects, efforts were ma de to develop 5-ASA products with other delivery systems to prevent proximal sm all-bowel absorption. Three such oral preparations are now available in the Un i ted States: two products containing mesalamine (Asacol, Pentasa), olsalazine sod ium (Dipentum) and balsalazide. Each uses a different mechanism to deliver the 5-ASA moiety to the sites of inflammation such as distal small bowel and colon, bypassing the absorption by jejunum.

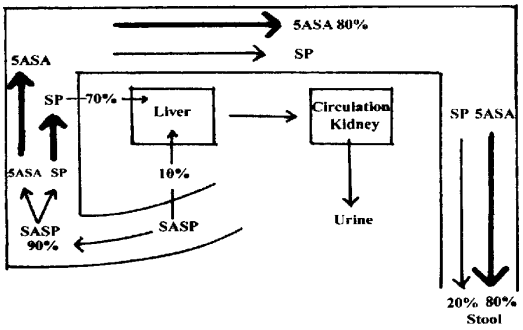

Figure 2 Metabolism and pharmacokinetics of salicylazo-sulfapyridine. Adopted from the Ph.D. thesis entitled, "Salicylazosul fapyridine Metabolism in Clinical Practice" submitted by Das KM to the University of Edinburgh, U.K., J anuary 1973.

Asacol(mesalamine) contains 5-ASA coated with an acrylic-based resin.Theres in releases 5-ASA in a pH-dependent manner at pH 6 or above. This causes releas e of 5-ASA in the distal small bowel and colon, making this drug ideal for the treatment of UC. Another mesalamine product, Pentasa, is 5-ASA encapsulated in ethylcellulose microgranules. This time-release formulation allows for release of 5-ASA throughout the small and large in testines. Thus, this drug appears to be superior for small bowel Crohn's disea se (CD) in addition to its use in UC. While these products are effective and safe, there have been rare reports of granulom atous hepatitis, interstitial neph ritis and recurrent thrombocytopenia on rechallenge with mesalamine/ mesal azine[4,5,6].

Olsalazine sodium consists of two molecules of 5 ASA linked by a diazo bond. B a lsalazide consists of 5-ASA linked with 4-amino-benzoyl-β-alan ine (an iner t compound) by a diazo bond. The presence of the azo bond in both of these comp ounds, similar to sulfasalazine's, prevents small-bowel absorption and allows for delivery of the drug mainly in the colon, where bacterial azo reductase libe rates the 5-ASA. These drugs would therefore be useful in the same circumstances as sulfasalazine. However, the 5-ASA products may cause diarrhea due to decreased water absorpti on in the small bowel, and this side effect occurs most frequently with olsalazine. Since the diseases these drugs are used to treat are diarrheal illnesses, their use may be limited by this untoward effect. In a recent study [7] bal salazide was found to be more effective and better tolerated than mesalamine as treatment for UC.

In the treatment of distal colitis, enema preparation of 5-ASA (Rowasa enema) is efficacious. In the initial study to identify the active moiety in sulfasalazi ne, patients with distal UC were treated with sulfasalazine, 5-ASA, or sulfapyr idine enemas[8]. Three quarters of the patients in the sulfasalazine and 5-ASA groups showed improvement, while only about one third of patients in the sulfapyridine grop improved. These data supported the hypothesis that 5-ASA was the active therapeutic moiety, and subsequent studies confirmed the efficacy of 5-ASA enemas in distal colitis[9]. 5-ASA is also available in suppo sitory form (Rowasa) that is beneficial for the treatment of proctitis.

Distal ulcerative colitis

About two thirds of the patients with proctitis and proctosigmoiditis respond to hydrocortisone enema (Cortenema) or 5-ASA enemas (Rowasa). However, in the pat ients with proctitis and/or proctosigmoiditis that do not respond to this conven tional treatment of hydrocortisone enema of 5-ASA enemas, several maneuvers are helpful. A clinical trial that compared the efficacy of nightly 4 g 5-ASA retention enemas with continued administration of 100-mg hydrocortisone enemas in distal UC after failure of a 3-week trial of the latter, with or without oral sulfasal azine, demonstrated that a significantly greater number of refractory patients responded to 5-ASA enemas than to continuation of standard therapy[10].

Several studies show that mesalamine enemas 4 g/day along with oral mesalamine 2 .4-4 g/day are useful in inducing and maintaining remission. The data also suggest that a higher dosage (such as 4 g/day orally) of all but one 5-ASA agent offers an important therapeutic advantage in some of the patients who are apparen tly "refractory" to conventional dosage. The exception to this is olsalazine, which, because of dimer-induced intestinal secretion, delivers more fluid to the colon and may cause diarrhea. Other data suggest that daily or every-other- day administration of 5-ASA enemas is sufficient to maintain remission, but that this effect is lost if administration is reduced to every third day.

A recent 6-week multi-center, randomized, double-blind comparative study of oral mesalamine versus rectal mesalamine versus combination therapy in the treat ment of mild-to-moderate distal UC evaluated the differences among these regimens. A total of 60 patients were enrolled in the study; patient demographics, in cluding UC history, did not differ significantly among treatment groups[11]. This study suggests that a combination of oral and rectal mesalamine in patients with mild-to-moderate UC produces earlier relief of rectal bleeding tha n either therapy alone and more complete relief of rectal bleeding than oral the rapy alone. 5-ASA by the oral route and intermittently by topical route was found to be more effective than oral

therapy alone in maintaining remission[12].

Glucocorticoids

Like sulfasalazine, glucocorticoids and adrenocorticotropic hormone(ACTH) have b een used in the treatment of UC for more than 40 years. The first controlled trial was done in 1955 by Truelove and Witts [13], and this, and other subs equent studies, clearly established the efficacy of glucocorticoids. Several stu dies have established that for mild-to-moderate disease, a daily dose of 40 mg of prednisolone is optimal, while for severe disease the optimal dosage is 60 mg of prednisolone or equivalent in divided doses. Even in severe disease, intravenous glucocorticoids have been shown to induce remission in up to 80% of patients. While ACTH is effe ctive, studies have shown that it has no significant benefit over glucocorticoids, and it is now rarely used due to its expense and the fact that it must be used intravenously. For distal colitis, local therapy with glucocorticoid enemas is effective. However, unlike sulfasalazine and 5-ASA compounds, glucocorticoids have not been found to have any benefit as long-term maintenance therapy in UC.

Because of the numerous systemic side effects of glucocorticoid therapy, attempts have been made to develop poorly absorbed, topically active steroids and gluco corticoids with high topical activity and high rate of metabolism in the liver. The most promising of these agents appears to be budesonide. It is readily absor bed from the gut and rapidly degraded to metabolites with low glucocorticoid sys temic activity during the first passage through the liver. It is not yet available in the United States, but several recent studies with oral administration suggest its efficacy in treating UC[14], and ileal Crohn's disease[15,16], as well as distal UC in the form of enemas[17,18].

In a randomized trial of Budesonide 8 mg/day vs prednisone 40 mg/day for 8 wk in patients with CD, there was equivalent remission by CDAI<150 in both groups. However, twice as many responders in the Budesonide groups responded to treatme nt with no side effects as compared to the prednisone group[19].

Immunosuppressive/immunomodulatory agents

The first immunosuppressive agents used in the treatment of IBD were 6-mercapt o purine (6-MP) and its *S*-imidazole precursor, azathioprine. Azathioprine was de veloped with the intent of allowing delayed release of 6-MP, which is the active metabolite. In clinical practice, azathioprine and 6-MP have similar efficacy and toxicity, and their use is usually based on personal preference and experience.

Several controlled and uncontrolled trials have been conducted to evaluate the efficacy of 6-MP (1-2 mg/kg body weight per day) and azathioprine which is metabolized in the liver and releases 6-MP. The overall results show a response rate of about 70%, with a significant steroid-sparing effect in most patients. In patients who stop taking these agents after remission is induced, the relapse rate is about two thirds[20,21].

The main impedance to use these agents by many gastroenterologists is the concer n of toxicity. While many patients receiving either agent may develop a decreased white blood cell (WBC) count, few develop marked leukopenia. Because of the potential for bone marrow suppression, blood counts must be checked frequently (e.g. initially bi-weekly and then once a month), but at the dosages used problems are rare. In one of the largest series reviewing the toxicity of 6-MP in infla mmatory bowel disease, the authors found marked bone marrow suppression in 2% of patients (WBC<2500/mm\+3), infections in 7.4%, and severe infections in 1.8%. Off note, however, many patients were receiving concomitant corticosteroids, an d it is unclear what role this may have played in the infections. Pancreatitis c an be seen in 3.3% of patients[22]. This is believed to be an allergic r eaction and usually occurs within 1 month of onset of therapy and abates on with drawal of the agent. Pancreatitis precludes further use of these drugs, while leukopenia may be supported with low-dose corticosteroids or by using a smaller dosage of 6-MP. Rarely, patients may develop a cholestatic hepatitis-like picture even after long term use. Therefore, periodic check-ups (about every 6 months) for liver function tests are necessary. Abnormal results are reversible after cessation of therapy.

A uheoretical risk with the use of purine analogues is teratogenicity and the de velopment of malignancy, particularly lymphoma. Although there have been occasional reports of malignancy in patients receiving 6-MP or azathioprine, little data support a causative effect in patients with IBD[23]. In reviews looking at teratogenicity, no difference in premature births or congenital anomalies was found in patients taking 6-MP compar ed with the general population[24].

Cyclosporine is an immunomodulatory agent that has shown some promise in refractory IBD. It acts by inhibiting T-lymphocyte function, does not have the myelos uppressive effects of the purine analogues, and produces an effect quickly, usually within 1 wk. The first report of cyclosporine use in IBD was in 1984, and multiple open trials for use in UC have been conducted since then.

Several recent trials have investigated the efficacy of cyclosporine. These stud ies, although with small patient numbers, indicate that cyclosporine, at least temporarily, and induced remission in up to 80% of patients with severe UC unresp onsive to corticosteroid therapy[25]. However, the majority of these patients do not sustain clinical remission with oral cyclosporine and eventually required colectomy before one year[26]. Recently, a study showed lower relapse rate with azathioprine maintenance therapy after remission was induced wit h intravenous cyclosporine[27].

Antibiotics

Antibiotics are not generally useful as a primary therapy for

UC. Although antib iotics do have a clear role in treating complications of UC, such as abscesses, they have never been shown to be efficacious as a direct treatment for the unde rlying disease[28].

A recent double blind, placebo controlled trial found that ciprofloxacin treatm ent was slightly better than placebo at 3 months but approached placebo without significant difference in response at 6 months in UC patients[29].

Nicotine

While UC is more common among the previous smokers, the efficacy of nicotine as a therapeutic agent in UC remains controversial[30,31]. Given the addictive property of nicotine and significant adverse effects on cardiovascular system and the lack of clear benefit in UC, nicotine cannot be recommended at this time[32].

Nutrition

Since UC is a condition of bowel inflammation, several investig ators have studied bowel rest as therapy. Total parenteral nutrition (TPN) allows for bowel rest, eliminates dietary macromolecules and, thus, reduces mucosal immune response, and helps to correct the malnutrition associated with UC. Several randomized controlled trials have looked at the benefit of TPN in active UC. They found that TPN offered no benefit over the control group with regard to UC[33]. Patients with distal colitis/proctitis should be on a high roughage diet [34] and those with anemia refractory to iron and vitamin supplements may benefit from treatment with oral iron and recombinant erythropoietin[35].

Other agents

Heparin was found to paradoxically induce remission in 9 of 10 patients with UC refractory to standard therapy [36]. It may act as an anti-thrombotic a gent or may be directly anti-inflammatory. Further multicenter studies are curr ently in progress to examine the efficacy of heparin in patients with active UC.

Deficiency of short-chain fatty acid (SCFA) is associated with diversion colitis, and studies with SCFA enemas in patients with distal UC showed good response in an initial study[37]although a subsequent study could not reproduce these data[38]. Further studies are warranted to explore this simplified treatment.

CROHN'S DISEASE

The management of CD is similar in many respects to the management of UC since the two diseases share many common features. However, there are differences.

Sulfasalazine and 5-ASA products

Being a transmural disease, the medical management of the inflammatory process in CD is often more difficult than it is in UC. Pharmacologically active compounds that exert their effect from the luminal side of the intestine as a local anti - inflammatory agent have limited response because of the lack of transmural ava ilability of the drug. Oral sulfasalazine or 5-ASA derivatives are commonly employed initially for the col onic manifestations of the disease. A multicenter study that evaluated the role of Pentasa in active CD demonstrated that a dose of 4 g/ day was more effective in inducing remission than placebo[39].

Glucocorticoids

Corticosteroids are often used on a short-term basis to manage acute exacerbati ons of the disease. However, intra-abdominal and perineal sepsis, common compli cating factors, must be ruled out before corticosteroids are administered. Oral budesonide (9 mg daily) treatment has been found to be useful to induce remissi on with less steroid-related side effects[40]. The efficacy was lower than prednisone[41]. Recently, budesonide (9 mg daily) was also found to be superior in inducing remission than mesalamine (2 g twice daily) over 16 wk of therapy in active ileocolonic CD[42]. However, on a long term bas is, (over 12 months), the use of budesonide (6 mg/ day) did not sustain clinical remission[43]. Further studies are currently in progress to ascertain th e dosage, duration and clinical response.

Immunosuppressive/immunomodulatory agents

In a double-blind placebo controlled study, 6-mercaptopurine (6-MP) was found to induce remission or significant clinical improvement in about two-thirds of patients with symptomatic CD[44]. If symptoms cannot be controlled with corticosteroids or if it is not possible to taper steroid dosage while maintai ning symptom control, then immunomodulatory agents such as azathioprine or 6-MP may be used in conjunction with reduced doses of steroids to induce and m aintain remission. 6-MP may be used in conjunction with reduced doses of steroids to induce and maintain remission. 6-MP has also been demonstrated to be effective in closing fistulas and reducing steroid requirements in patients with CD. Unfor tunately, fistulas frequently recur upon cessation of immunosuppressive treatment[44]. IV loading of 6-MP has not been shown to decrease the time to re spond in patients requiring ongoing steroid therapy for Crohn's disease. However, Casson has a report of a rare response of IV 6-MP in patients with fulminant colitis who failed steroid management and refused to have surgery[45,46]. Cyclosporine and methotrexate have been found to be benefi cial in subgroup of patients with chronically active CD[47,48]. Tacrolim us (FK506) has a mechanism similar to cyclosporine and preliminary results have shown some benefits to proximal small bowel or fistulizing CD[49]. In a recent small study, 7 of 11 patients with steroid refractory Crohn's disease and UC, tacrolimus with azathioprine and mesalamine achieved rapid remission and allowed for tapering of steroids[50]. However, the dat a related to the use of these drugs is very limited, and at this time, these drugs may be considered in a subgroup of patients who are refractory to more conven tional treatment.

Nutrition

Low residue diets have been found to be beneficial in patients with CD[51]. In patients with proximal CD there was a significantly increased incidence of lactose malabsorption[52]. A defined formula diet can induce remission, probably through a decrease in immunostimulation by luminal contents[53]. This treatment is controversial because remission lasts only as long as the diet is continued. Because fishoil has anti-inflammatory actions, studies have shown a reduction in relapse rates in CD, but its use is limited by the unp leasant taste and smell[54].

Antibiotics

Antibiotics (metronidazole, ciprofloxacin, and clarithromycin and trimethoprimsu lfamethoxazole) can be useful intreatment of CD[55,56]. Antibiotics are also used to treat complications such as intra-abdominal sepsis and perineal fistulas. Although long-term use of antibiotics for treatment of CD has been advo cated by some physicians, there is no convincing support for this strategy.

Maintenance of remission in CD

One of the most vexing issues in the treatment of CD is maintaining remission. The recent data come from trials that compare maintenance regimens following surgical resection. Both mesalamine and metronidazole have been useful in prolonging the time from surgery to symptomatic relapse[57,58,59].

A meta-analysis of sulfasalazine and 5-ASA for maintenance therapy of CD demon strated that 5-ASA was more likely to maintain remission than sulfasalazine and that it demonstrated greater efficacy for patients with ileal desease than for those with combined ileocolonic disease; ileocolonic disease responded better than colonic disease[60].

Although oral mesalamines have demonstrated some benefit in maintaining remission, there are many unresolved issues, e.g. which mesalamine preparation is prefer able, in which clinical group such as phlegmonous type, stricture type or perfor ating type of CD, what dose should be used, and whether drugs are equally effect ive in maintaining remissions induced initially by medical and/or surgical interventions. A recent study suggested that 6-MP is also effective in preventing post-operative recurrence of CD and may be more effective than 5-ASA preparation s[61].

Newer agents

Tumor necrosis factor (TNF-α) is a proinflammatory cytokine present in excess in the mucosa of patients with active CD. A chimeric mouse/human an ti-TNF-α monoclonal antibady (cA2, infliximab, Remicade; Centocor, Malvern, PA)was developed and its efficacy was assessed in patients with severe CD[62]. There was no apparent dose relation between 5 mg per kg to 20 mg per kg body weight given as intravenous infusion as a single dose over a 2 h period. After a single dose of infusion 5 mg/kg clinical response was achieved in 65% of the patients. About half of these patients in the treatment group (compared with 4% in the placebo group) went into remission by wk 4. However, by wk 12, the number of patients maintaining their clinical response after the single dose infusion had decreased to 41% (compared to 12% in the placebo group). Repeated doses in initial responders appear to maintain remission at least in the short term study reported so far. The patients with no response to the first infusion of cA2 were less likely to have a response to a second infusion. Thus, this group of patients may clinically differ from the responder group. Preliminary results from another anti-TNF antibody (CD P571) also showed promising results[63]. The adverse effects of cA2 therapy were mostly transient and not serious and they included headache, nausea, upper respiratory tract infection, fatigue, myalgia, rhinitis, pain, pruritus and dyspnea[62]. Of the 29 patients who received two cA2 infusions, two had a reaction with chest pain, dysp nea and nausea necessitating discontinuation of the infussion. At least 6 % of t he patients developed anti-cA2 antibody by 12 wk. This percentage may be hig her because cA2 was still detectable in serum samples in two-thirds of the pati ents and the presence of cA2 may have interferred with the anti-cA2 assay. As use of infliximab has increased, reports of hypersensitivity have been published. In our experi ence, this can be avoided by premedication with benadryl and glucocorticoids[64]. It is unknown at this time whether the presence of anti-cA2 will in fluence the efficacy of the therapy, particularly after subsequent infusions. Remi cade has recently been approved by the FDA for use in moderate and severe Crohn's disease, with or without fistula since closure of fistula has also been reported with this therapy. In another review, infliximab was effective in achi eving fistula closure 68% *vs* 26% placebo[64].

Interleukin-10 (IL-10) is a cytokine with both anti-inflammatory as well as immunosuppressive properties. In a recent study in patients with steroid-refractory active CD, daily administration of IL-10 for one week resulted in 50% of p atients achieving complete remission within 3 wk (compared to 23% in the placebo group)[65].

IL-11 has been known to have a mucosal protective effect. Besides its anti-inf lammatory effects, it also has a trophic effect on intestinal villi. Sands *et al* are currently investigating dosing strategies for possible use of this cyto kine in the treatment of active Crohn's disease[66,67].

Intercellular adhesion molecule-1 (ICAM-1)is an inducible transmembrane glycop rotein involved in the activation of leukocytes and is upregulated in inflamed m ucosa in CD. ISIS 2302 is a 20-base phosphorothioate oligodeoxynucleotide whic h selectively inhibits cytokine-induced ICAM-1 expression. In patients with steroid-resistant active CD, it was found to achieve remission in 7 of 15 patients immediately after treatment and 5 of 7 patients were still in remission at the end of six months[68]. This modality of treatment opens upyet anoth er novel

approach of administering antisense therapy for IBD.

It is recognized that NSAIDs may be harmful in patients with inflammatory bowel disease. Since the arrival of COX_2 inhibitors on the market, only one study has attempted to evaluate their safety in IBD. The results do not point to any ad vantage or safety of COX_2 drugs over NSAIDs[69].

Probiotics

There has been recent investigation into the bacterial makeup and possible assoc iation of intestinal bacteria with inflammation. Investigators have focused on use of nonpathogenic *E.coli* and other probiotic preparations in maintaining remis sion of UC. In one study by Rembacken *et al* at 12 months there was a non-st atistically significant difference between two groups, one taking mesalamine, the other taking nonpathogenic *E.coli*[70,71].

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