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A Review on Inflammatory Bowel Disease and their Treatment

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Abstract: ***Inflammatory Bowel Disease is characterised by chronic inflammation of the gastrointestinal tract and affect patient's quality of life. Treatment of IBD involves induction and maintenance of remission. Current available therapies include anti-inflammatory, amino salicylate, corticosteroids, immunosuppressive agent, antibiotics, and biological agent are available. Oxidative stress could be a major contributing factor to the tissue injury and fibrosis that characterised Crohn's disease. Decreased blood level of vitamin C and E and decreased intestinal mucosal levels of CuZn superoxide dismutase, glutathione, vitamin A, C, E and β-carotene have been reported for Crohn's patients. The reduction of brush border enzymes with normal cytoplasmic enzyme in the presence of abnormal morphometry is further evidence of concept of Crohn's disease as a diffuse lesion of the gastrointestinal tract. There has been considerable research in the colonic delivery system and targeting has been achieved by several ways. The primary approach to the colonic delivery of the drug include prodrugs, coating with pH sensitive and time dependant polymers. Eudragit L-100 and Eudragit S-100 are used as an enteric coating material to keep the multi-particulate intact and to release the drug in stomach and upper intestine and produce local and systemic drug effect at the site of colon.***

Keywords: Crohn's Disease, Inflammatory Bowel disease, Enzymes, Antibiotics

1. Introduction

Inflammatory Bowel Disease (IBD) describe two distinct idiopathic inflammatory disorder of the intestine, Ulcerative colitis and Crohn's disease. Ulcerative colitis is characterised by period of active and inactive disease, a pattern observed in 80-90% of patient with this disease [1]. Inflammatory Bowel Disease comprise Ulcerative Colitis (UC) and Crohn's Disease (CD), relapsing and remitting disease characterise by chronic gastrointestinal tract inflammation [2]. Crohn's disease is debilitating illness of the bowel characterised by chronic inflammation of unknown etiology [3]. The mucosal enzyme studies demonstrated that patient with Crohn's disease had a significant reduction in brush border enzyme (disachharidase) but no change in cytoplasmic enzyme activity (Dipeptidase). The enzyme level in patients with ulcerative colitis did not differ from the healthy controls. The reduction of brush border enzymes with normal cytoplasmic enzymes in the presence of abnormal morphometry is further evidence of the concept of Crohn's disease diffuse lesion of the gastrointestinal tract [4].

Sources and Selection Criteria

Literature was retrieved using the key words 'Ulcerative colitis', 'Crohn's disease'or 'Inflammatory Bowel Disease'. Medication treatment classes and specific agent names were also included as search term (e.g. amino salicylate, mesalazine, corticosteroids, prednisolone, budesonide, etc.). Additional resources were identified through hand searches of bibliography of current articles. Some targeted drug delivery also involve to produce local and systemic effect at the site of colon.

Goal of Therapy

The colon is an ideal site for protein and peptide absorption. Acidic and enzymatic degradations are major obstacles in the oral administration of peptide drugs, but by targeting to the colon, the proteolysis can be minimized. Colon targeting had application in several therapeutic areas such as colon cancer, ulcerative colitis, irritable bowel syndrome, or the administration of drugs that are adversely affected by upper gastrointestinal tract (GIT). The primary approach to the colonic delivery of the drug included prodrugs, coating with pH-sensitive and time dependent polymers. Eudragit L-100 and Eudragit S-100 are used as an enteric coating material to keep the multi-particulates intact and not to release the drug in stomach and or upper intestine [5]. In patient with acute symptoms of IBD, the goals is to induce clinical remission of syndrome while improving quality of life. Following attainment of remission, treatment is tailored to maintain remission. Additional goals of therapy include reducing long term steroids use and in the case of UC, mitigating long term risk of colorectal cancer (CRC). Choice of therapy is based on disease severity and location as well as intestinal and extra-intestinal manifestation. If induction therapy fails to control syndrome within a reasonably trial period, another therapeutic approach should be trialled until symptoms are controlled and maintenance therapy can be initiated [6]. Aim of the current study was to investigate the role of demographic, disease specific characteristic and different treatment regimen on HRQoL of patient with IBD, either Crohn's disease (CD) or Ulcerative Colitis (UC) [7]. 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 hospitalisation, reduce need for surgery and lower rates of disease complication. While there is agreement that mucosal healing should be consider, consensus is lacking regarding the most effective means of measuring it, and the magnitude of healing require to alter disease course is uncertain [8].

Current Treatment Options

Pharmacological agent are the mainstay of therapy for the induction and maintenance of IBD remission with surgical intervention as needed. The choice of pharmacological

therapy is based on disease severity and location and desired to minimise adverse effects. Owing to the waxing and waning nature of IBD, long term maintenance therapy is often required.

Symptoms of IBD

Extra-intestinal symptoms of CD related to intestinal inflammation include spondyl arthritis (ankylosing spondylitis and sacroilitis), peripheral arthritis, cutaneous manifestations (erythema nodosum and pyodermagangrenosum) ocular inflammation (uveitis, episcleritis or sclera-conjunctivitis), primary sclerosing cholangitis and hypercoagulability. In addition, CD may also be complicated by sequelae related to malabsorption (e.g. anemia, cholelithiasis, nephrolithiasis or metabolic bone disease). There has also been an increased awareness that CD of long duration can be complicated by adenocarcinoma of GI tract. There has ilium and colon are the most frequently affected sites, commonly complicated by intestinal obstruction, inflammatory mass or abscess. There is acute presentation of ileitis may mimic appendicitis and rarely CD may be limited to the appendix. In contrast to ulcerative colitis, perianal manifestation are unique to CD and may precede the onset of bowel symptoms. Patient with CD limited to the colon typically present with rectal bleeding, perianal complication and extra-intestinal complication involving the skin or joints. CD limited to the colon can be difficult to distinguish from ulcerative colitis. Diffuse jejunoileitis is a less common variant often complicated by multiple stenosis, bacterial over growth and protein losing enteropathy [9].

Quality of Life

There is general consensus among physicians that UC refractory to medical management require surgical intervention with colectomy. The issue become more complex in patient who are currently in remission, but are trouble by flare with the need for frequent hospital admissions. Quality of life analyses were conducted using the IBDQ, a visual analog scale (VAS), and the Oresland scale. The patient treated with CSA reported a better ability to sleep, better stool consistency, less abdominal or rectal pain (VAS), and fewer day time, night time (Oresland), and daily trips to the toilet (VAS) than the surgical patients. The mean number and rate of hospitalizations within the first year was also lower in the CSA patients [10]. It consisted of question that related to bowel function, work, social life and sexual activity. The questionnaire also aimed to identify restriction the condition had imposed on diet, leisure and social pursuit. The technique of restorative proctocolectomy with IPAA included both mucosal proctectomy and pull through IPAA in the earlier part of the series and a stapled anastomosis constructed 1.5 to 2.0 cm above the dentate line in the later phase. Each patient received a temporary ileostomy that was closed 8 to 12 week later [10].

Immunosuppressant

The antimetabolites, azathioprine and 6-mercaptopurine are purine analogue that interfere with nucleic acid metabolism by acting as substrate competitive antagonist, resulting in immunosuppression and reduce cell proliferation. 6-mercaptopurine was first synthesized in 1951 and initially used to treat leukaemia. Azathioprine, its S-substituted precursor, was synthesized in 1957. Azathioprine has a longer half-life and a different spectrum and perhaps lower level of adverse event than 6-mercaptopurine, but there are no comparative trials in humans. Onset of action is delayed for up to 3 to 4 month of treatment. Toxicity, the risk for severe bone marrow suppression in particular is increased in patient with thiopurine-S-methyltransferase (TPMT) deficiency, which occurs in 0.3% of general population respectively. The use of azathioprine for the treatment of quiescent ulcerative colitis was first reported in 1996. A survey conducted by Hilsden 2003 showed that 12% of the patient members of the Crohn's and colitis Foundation of Canada who are diagnosed with ulcerative colitis are treated with azathioprine or 6-mercaptopurine. Other survey have shown that 77% of gastroenterologist in Europe and North America and up to 93% of British consultant gastroenterologist use azathioprine for the treatment of ulcerative colitis. The common practice of using azathioprine or 6-mercaptopurine for maintenance of remission in ulcerative colitis, however, is based on limited data. Although evidence exist to support the use of azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis remain controversial [11]. One small study (36 participant) found no difference in maintenance of remission rates at one year between combination therapy with azathioprine (2.5mg/kg/day) and infliximab (5mg/kg every 8 weeks) compare to infliximab mono-therapy. A GRADE analysis indicated that the overall quality of the evidence supporting this outcome was very low due to very sparse data (29 events) and high risk of bias. An adequately powered trial would be necessary to allow for any conclusion regarding the role of azathioprine as an adjunctive to infliximab maintenance therapy in Crohn's disease. There is moderate quality evidence that combination therapy with azathioprine and infliximab is superior to infliximab mono-therapy for induction of remission in moderate to severe Crohn's disease. Furthermore therapy with azathioprine and 6-mrcaptopurine may help to prevent the development of antibodies to infliximab. The development of antibodies to infliximab has been associated with infusion reaction and loss of responses to infliximab. An analysis of the ACCENT 1 induction trials data found that patient who received therapy with azathioprine, 6mercaptopurine or methotrexate in conjunction with infliximab had significant lower chance of developing antibodies to infliximab than patient received infliximab mono-therapy. Further maintenance trials assessing combination therapy should evaluate the interaction between antimetabolite (azathioprine or 6-mercaptopurine) therapy and infliximab with respect to antibody formation and efficacy.

One study (147 participants) failed to show any significant benefit for early azathioprine treatment over a conventional management strategy. In the early azathioprine treatment group 67% (11-85%) of trimesters were spent in remission compare to 56% (29-73%) in the conventional management group. The result of this need to be confirmed by another study. Further research is required to determine optimal management strategies for patients with quiescent Crohn's disease [12].

Antibiotic

Treatment of acute pouchitis- The results of one small study (16 participants) suggest that ciprofloxacin may be more effective than metronidazole for treatment of acute pouchitis. One hundred percent (7/7) of ciprofloxacin patients achieved remission at two weeks compared to 33% (3/9) of metronidazole patients. A GRADE analysis indicate that the overall quality of the evidence supporting this outcome was very low due to high risk of bias and very sparse data (10 event). There was no difference in the proportion of patient who had at least one adverse event (RR 0.18, 95% CI 0.01 to 2.98). Adverse events included vomiting, dysgeusia or transient peripheral neuropathy. There were no difference between metronidazole and budesonide enemas in terms of clinical remission, clinical improvement or adverse events. Adverse event included anorexia, nausea, headache, asthenia, metallic taste, vomiting, paraesthesia and depression. There were no difference between rifaximin and placebo in terms of clinical remission, clinical improvement or adverse event. Adverse event included diarrhoea, flatulence, nausea, proctalgia, vomiting, thirst, candida, upper respiratory tract infection, increased hepatic enzyme and cluster headache. There was no differences in clinical improvement between *Lactobacillus GG*and placebo. The result of these studies are uncertain due to very low quality evidence.

Treatment of chronic pouchitis- A pooled analysis of two studies (76 Participant) suggest that VSL#3 may be more effective than placebo for maintenance of remission. Eighty-five percent (34/40) of VSL#3 patient maintained remission at 9 to 12 months compare to 3% (1/36) of placebo patients (RR 20.24, 95% CI 4.28 to 95.81) A GRADE analysis indicated that the quality of evidence supporting this outcome was low due to very sparse data (35 event). Adverse events included abdominal cramps, vomiting and diarrhoea. There was no difference in effectiveness between glutamine and butyrate suppositories for maintenance of remission. There was no difference in clinical improvement or adverse event rates between bismuth carbomer foam enemas and placebo. Adverse event included diarrhoea, worsening symptoms, cramping, sinusitis and abdominal pain. The result of these study are uncertain due to very low quality evidence [13].

For acute pouchitis, very low quality evidence suggests that ciprofloxacin may be more effective than metronidazole. For chronic pouchitis, low quality evidence suggest that VSL#3 may be more effective than placebo for maintenance of remission. For the prevention of pouchitis, low quality evidence suggest that VSL#3 may be more effective than placebo. Well design, adequately powered studies are needed to determine the optimal therapy for the treatment and the prevention of pouchitis [13].

Salicylate

Drug that are incorporate the 5-aminosalicyllic acid (5-ASA) moiety are commonly used to treat inflammatory bowel disease. In recent years, several different formulation of 5-ASA products have been developed to improve tolerability and facilitate adherence to the regimen. Hypersensitivity to these products has been described, including rash, fever, pneumonitis, interstitial nephritis and gastrointestinal symptoms [14]. Oral 5-amino salicylic acid (5-ASA) preparation were intended to avoid the adverse effects of sulfasalazine (SASP) while maintaining its therapeutic benefits. Previously it was found that 5-ASA drugs in dosage of at least 2g/day, were more effective than placebo but no more effective than SASP for including remission in ulcerative colitis [15].

Corticosteroids

The use of glucocorticosteroids to treat both Crohn's disease and ulcerative colitis is widespread, but no systematic review and meta-analysis has examined the issue of efficacy of these agent in its entirety. Standard glucocorticosteroids are probably effective in including remission in UC and may be of benefit in CD. Budesonide induces remission in active CD, but is less effective than standard glucocorticosteroids and is of no benefit in preventing CD relapse. Glucocorticosteroids drug were first used over 60 years ago, and the first controlled trial demonstrating their efficacy in patients with active inflammatory bowel disease was conducted in the 1950s. Because of their widespread use in the treatment of inflammatory bowel disease (IBD), information concerning both the efficacy and adverse event with these agent is important for patients and clinician [16].

Corticosteroids are first line therapy for induction of remission in ulcerative colitis. Although corticosteroids may improve symptoms, they have significant adverse effects. Steroids which act topically with less systemic side effect may be more desirable. Moderately quality evidence to supports the use of oral budesonide at a 9mg daily dose for induction of remission in active ulcerative colitis, particularly in patients with left sided colitis. Budesonide 9mg daily is effective for induction of remission in the presence or absence of concurrent 5-ASA therapy. Further, budesonide appears to be safe and does not lead to significant impairment of adrenocorticoid function compare to placebo [17]. Budesonide is more effective than placebo for induction of remission in Crohn's disease. Although short term efficacy with budesonide is less than with conventional steroids, particularly in those with severe disease or more extensive colonic involvement, the likelihood of adverse event and adrenal suppression with budesonide is lower. The current evidence does not allow for afirm conclusion on the relative efficacy of budesonide compare to 5-ASA products [18].

TNF Blocker

Infliximab, an anti- TNF antibody, has been approved recently by the US FDA for the

Treatment of ulcerative colitis to reduce signs and symptoms, to induce clinical remission and healing of the intestinal mucosa, and to eliminate the use of corticosteroids in patients presenting with moderately-to-severely active ulcerative colitis without adequate response or who are intolerant or have medical contraindication to therapy with corticosteroids or immune modulators. It is the only anti-TNF agent that has been approved for treatment in ulcerative colitis. Induction therapy with infliximab consist of 3 intravenous infusions at the dose of 5mg/kg over 2h at 0, 2 and 6 weeks. Prior to that therapy many physician initiate treatment with corticosteroids or AZA/6-MP in order to

reduce the formation of antibodies to infliximab (ATI). Maintenance treatment is recommended every 8 weeks when responses to induction therapy is observed. If there is no responses to the initial therapy, further treatment with infliximab is not recommended [19]. Currently there are three anti-TNF agents approved by the US FDA for the induction and maintenance treatment of moderate to severe active luminal Crohn's disease, namely infliximab, adalimumab and certolizumab pegol are administered as subcutaneous injection. Treatment with adalimumab consist of initial injection of 160mg followed by an 80mg dose given week later with initiation of maintenance treatment after 2 weeks at a dose 40mg every 2 weeks. Treatment with certolizumab pegol with a subcutaneous injection of 400mg at a week 0, 2 and 4 is followed by maintenance treatment every 4 weeks [19].

In the ACCENT 1 trial, we target to assess the efficacy and safety of repeated infusion of infliximab in patient who improved after an initial infusion. Our hypothesis was that maintenance infliximab treatment is a more effective intervention than a single infusion. Secondary objective included the assessment of infliximab corticosteroid sparing effects and safety in a large number of patients [20]. Tumor necrosis factor a (TNF-α) is a key proinflammatory cytokine in patient with Crohn's disease but is also found in increased concentration in the blood, colonic tissue and stool of patients with ulcerative colitis. However, the role of TNF-α in the pathogenesis of ulcerative colitis has been debated. Infliximab, a chimeric IgG1 monoclonal antibody, binds with high affinity to TNF-α neutralizing its biological activity. Infliximab therapy is effective for the induction and maintenance of clinical remission. However, the few small studies of infliximab in patients with active ulcerative colitis have yielded conflicting result [21].

Leukocyte Adhesion Inhibitors

The migration of leukocyte into inflamed intestinal tissue is highly regulated by specific molecular mechanism. Vedolizumab a humanised monoclonal antibody that specifically recognizes the α4 β7 heterodimer, selectively blocks gut lymphocyte trafficking without interfering to the central nervous system. Natalizumab and Vedolizumab differ in that Natalizumab blocks lymphocyte trafficking to multiple organs including the brain and gut. Vedolizumab was more effective than placebo as induction and maintenance therapy for ulcerative colitis. (Funded by Millennium Pharmaceutical; GEMINI 1 Clinical Trials.gov number, NCT00783718) [22].

Faecal Micro-biota Transplant

The intestinal micro-biota is involved in the pathogenesis of inflammatory bowel disease (IBD). Faecal micro-biota transplantation (FMT) has been used for the management of IBD as well as infectious diarrhoea. There is increasing evidence supporting a microbial influence in the pathogenesis of IBD resulting from an inappropriate immune responses toward component of the commensal micro-biota. Although there is inconclusive evidence for a specific pathogen causing IBD with a decrease in formicates such as *Bifidobacteria, lactobacillus and Faecali bacterium prausnit zii* and an increase in mucosal adherent bacteria [23]. The treatment of IBD is rapidly evolving and many conventional and novel drug treatment have proven efficacy including steroids, amino salicylate, immune-suppressants and biological therapy. An additional alternative treatment for the management of IBD is faecal micro-biota transplantation (FMT), which is transfer of gastrointestinal micro-biota from a healthy donor via infusion of a liquid stool suspension to restore the intestinal micro-biota of a disease individual. Faecal micro-biota transplantation is also being used as a therapy in IBD with report of patient with positive outcomes. However, there is currently a lack of cohesive assimilation of the available information on which to inform future robust clinical trials [23].

Probiotic

Evidence exist for the pathogenic role of the enteric flora in inflammatory bowel disease. Probiotics contain living micro-organism which exerts health effect on the host. We compare the efficacy in maintaining remission of the probiotic preparation *Escherichia Coli* and established therapy with mesalazine in patient ulcerative colitis. Growing evidence exist for a role of the intestinal micro-flora in the pathogenesis of inflammatory bowel disease (IBD). Findings from genetically engineered animal models as well as clinical observation have elucidated the importance of commensal bacteria. Antibacterial treatment showed some beneficial effects but the use of antibiotics is limited. Therefore, treatment with probiotics has been proposed. Probiotics are viable non-pathogenic micro-organisms that confer health benefited to the host by improving the microbial balance of the indigenous micro-flora. Apart from anecdotal experience, two controlled studies with the probiotics bacterial strain *Escherichia Coli*Nissle 1917 (EcN) in UC already exist. These trials showed no difference between the relapse preventing effects of EcN and standard mesalazine. However, some criticism was raised as to the validity of these studies. The present study was undertaken to confirm that the relapse preventing effect of probiotic therapy with EcN and standard mesalazine are equivalent [24].

2. Conclusion

IBD is a common disorder with profound effect on morbidity and a patient QoL. Despite advancement in the last decade, a substantial number of patient are not fully responsive to treatment or lose efficacy over time. Recent approvals and novel therapies in development offer alternative to existing therapies for IBD with the hope that in the near future more patient can attain disease remission. It is also found that there is enzyme deficiency at the brush border of small intestine. Lack of enzyme causes abdominal morbidity. The enzyme supplement can be fulfil the requirement when level of enzyme decreases in gastrointestinal tract.

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