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Drug Therapy in Ulcerative Colitis

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1. Introduction

The two primary types of inflammatory bowel disease (IBD) are ulcerative colitis (CU) and Crohn's disease (CD). These two diseases have many similarities and sometimes are difficult to distinguish from each other. However, there are several differences. UC is an inflammatory destructive disease of the large intestine characterized by motility and secretion disorders. Inflammation usually occurs in the rectum and lower part of the colon, but it may affect the entire colon. UC rarely affects the small intestine except for the end section, called the terminal ileum. UC may also be called colitis or proctitis. Inflammation makes the colon empty frequently, causing diarrhea. Ulcers formed in places where the inflammation has killed the cells of colon, bleeding ulcers and pus discharge. UC is an IBD that causes inflammation in the small intestine and colon. UC can be difficult to diagnose because its symptoms are similar to other intestinal disorders and another type of IBD called CD. CD differs from UC because it causes deeper inflammation within the intestinal wall. Also, CD usually occurs in the small intestine, although it can also occur in the mouth, esophagus, stomach, duodenum, large intestine, appendix, and anus. UC may occur in people of any age, but most often it starts between ages of 15 and 30, or less frequently between ages of 50 and 70. Children and adolescents sometimes develop the disease. UC affects men and women equally and appears to run in some families. Clinical and epidemiological data do not support a simple Mendelian model of inheritance for IBD. In its place CD and UC are considered to be complex polygenic diseases. UC is a chronic disease in which the large intestine becomes inflamed and ulcerated (pitted or eroded), leading to flare-ups (bouts or attacks) of bloody diarrhea, abdominal cramps, and fever. The long-term risk of colon cancer is increased [1-4].

The etiology is unknown for ulcerative colitis (UC). The consensus is so far that it is a response to environmental triggers (infection, drugs, or other agents) in genetically susceptible individuals. The genetic component is not as strong in UC as it is in CD. However, 10%-20% of patients with UC have at least one family member with IBD [1,2]. There are marked differences between ethnic groups with some (such as Ashkenazi Jews) having a particularly high incidence. Non-steroidal anti-inflammatory drugs may cause an episode of acute active disease in some patients with IBD. UC primarily affects young adults, but it can occur at any age from five to eighty years and women tend to be more commonly affected than men. It is a worldwide disorder with high-incidence areas that include United Kingdom, the United States, northern Europe and Australia. Low-incidence

areas include Asia, Japan, and South America. The causes of UC remain unknown. The major theories include infection, allergy to food component, genetics, environmental factors, and immune response to bacteria or other antigens [1]. Typical symptoms during flare-ups include abdominal cramps, an urge to move the bowels, and diarrhea (typically bloody). The diagnosis is based on an examination of the sigmoid colon using a flexible viewing tube (sigmoidoscopy) or an examination of the large intestine using a flexible viewing tube (colonoscopy). People who have had UC for a long time may develop colon cancer. Treatment is aimed at controlling the inflammation, reducing symptoms, and replacing any lost fluids and nutrients. UC may start at any age but usually begins between the ages of 15 and 30. A small group of people have their first attack between the ages of 50 and 70. UC usually does not affect the full thickness of the wall of the large intestine and hardly ever affects the small intestine. The disease usually begins in the rectum or the rectum and the sigmoid colon (the lower end of the large intestine) but may eventually spread along part or all of the large intestine. UC, which is confined to the rectum, is a very common and relatively benign form of UC. In some people, most of the large intestine is affected early on.
Ulcerative colitis (UC) affects about one in 1000 people in the Western world. Peak incidence is between the ages of 10 and 40 years. UC may affect people of any age and 15% of people are over the age of 60 at diagnosis [1-4]. The incidence of UC in North America is 10-12 cases per 100,000, with a peak incidence of UC occurring between the ages of 15 and 25. There is thought to be a bimodal distribution in age of onset, with a second peak in incidence occurring in the 6th decade of life. The disease affects females more than males with highest incidences in the United States, Canada, the United Kingdom, and Scandinavia. Higher incidences are seen in northern locations compared to southern locations in Europe and the United States.
Epidemiologic data support genetic contribution to the pathogenesis of IBD. Recently, numerous new genes have been identified to be involved in the genetic susceptibility to IBD [5]: TNF-308A, CARD15 (NOD2), MIF-173 gene, N-acetyltransferase 2 (NAT2), NKG2D (natural killer cell 2D), STAT6 (signal transducer and activator of transcription 6), CTLA-4 (cytotoxic T lymphocyte antigen-4), MICA-MICB (major histocompatibility complex A and B), HLA-DRB1 gene, HLA class-II gene, IL-18 gene (interleukin-18 gene), IL-4 gene, MICA-A5, CD14 gene, TLR4 gene, Fas-670 gene, p53 gene and NF-kappaB. The characterization of these novel genes is potential to identify therapeutic agents and clinical assessment of phenotype and prognosis in patients with IBD (UC and CD). The diagnosis of UC is made from the patient's medical history, a stool examination, sigmoidoscopy findings, and biopsy of specimens from the rectum or colon.

2. Drug treatment

The goals of treatment of UC are to induce and maintain remission of symptoms and inflammation of the inner lining of colon [2, 4, 6, 7]. Treatment options are determined according to the extent of the inflammation and the severity of the disease. Some people have long periods of remission, which can last for years. Unfortunately, the disease usually recurs periodically during an individual's lifetime. Predicting when a flare-up may occur is not possible, but early recognition of symptoms results in a better response to treatment. Patients with this disease are divided into three groups based on the site of involvement, which is important for treatment and prognosis. (1) Proctitis (involving the rectum, the last part of the colon near the anus); (2) Left-sided colitis (from the rectum to the splenic flexure — the area below the ribs on the left side); (3) Pancolitis (involvement more extensive than

the above two). Therapy for UC is aimed at quieting inflammation or relieving symptoms. It can usually control symptoms, but surgery may be required when conservative therapy fails or if signs of colon cancer develop.

Both medications and surgery have been used to treat UC. However, surgery is reserved for those with severe inflammation and life-threatening complications. There is no medication so far that can cure UC. Patients with UC will typically experience periods of relapse (worsening of inflammation) followed by periods of remission lasting for months to years. During relapses, symptoms of abdominal pain, diarrhea, and rectal bleeding can worsen patients' quality of life. During remissions, these symptoms subside. Remissions usually occur because of treatment with medications or surgery, but occasionally they occur spontaneously. Since UC cannot be cured by medications, the goals of treatment with medications are to induce remissions, maintain remissions, minimize side effects of drugs, and improve the quality of life. The treatment of UC with medications is similar, though not always identical, to the treatment of CD. Medications treating UC include anti-inflammatory agents such as 5-ASA compounds, systemic and topical corticosteroids, and immunomodulators [2, 8-10].

Anti-inflammatory medications that decrease intestinal inflammation are analogous to arthritis medications that decrease joint inflammation (arthritis). The anti-inflammatory medications used in the treatment of UC are topical 5-ASA compounds such as sulfasalazine (Azulfidine), olsalazine (Dipentum), and mesalamine (Pentasa, Asacol, Rowasa enema) that need direct contact with the inflamed tissues in order to be effective. Systemic corticosteroids can decrease the inflammation throughout the body without direct contact with the inflamed tissue. Systemic corticosteroids have predictable side effects in long-term treatment. Immunomodulators are medications that suppress the body's immune system either by reducing the cells that are responsible for immunity, or by interfering with proteins that are important in promoting inflammation. Immunomodulators are increasingly becoming important for patients with severe UC who do not respond adequately to anti-inflammatory agents. Examples of immunomodulators include 6-mercaptopurine (6-MP), azathioprine, methotrexate, and cyclosporine. There are drugs (including selected side effects and comments) that reduce bowel inflammation in Table 1[2, 8-11].

2.1 Anti-inflammatory drugs

Anti-inflammatory drugs are often the first step in the treatment of UC. Sulfasalazine (Azulfidine) can be effective in reducing symptoms of ulcerative colitis, but it has a number of side effects, including nausea, vomiting, heartburn and headache. This medication can not be given if the patients are allergic to sulfa medications. To evaluate the role of multi-matrix system (MMX) mesalamine in the treatment of UC, literature was obtained through searches of MEDLINE (1966-October 2007) and a bibliographic review of published articles. Key terms used in the searches included UC, mesalamine, MMX, SPD476, and Lialda. All English-language articles that were identified through the search were evaluated. The standard treatment for the induction and maintenance of remission in patients with mild-to-moderate UC is aminosalicylate products (mesalamine, sulfasalazine, balasalazide, olsalazine). Current mesalamine formulations are not ideal for long-term treatment due to issues with patient adherence secondary to complex dosing regimens and high pill burden. Clinical studies show that MMX mesalamine achieves clinical and endoscopic remission more frequently compared with placebo or mesalamine enema. Therefore, MMX mesalamine is an option in patients with UC. The cost of MMX mesalamine is comparable to that of oral and rectal formulations of mesalamine [11, 12].

Drugs	Selected Side Effects	Comments
Aminosalicylates		
Sulfasalazine	Common: Nausea, headache, dizziness, fatigue, fever, rash, reversible male infertility. Uncommon: Inflammation of the liver (hepatitis), pancreas (pancreatitis), or lung (pneumonitis); hemolytic anemia.	Abdominal pain, dizziness, and fatigue are related to dose; hepatitis and pancreatitis are unrelated to dose.
Balsalazide Mesalamine Olsalazine	Common: Fever, rash. Uncommon: Pancreatitis, inflammation of the pericardium (pericarditis), pneumonitis For olsalazine: Watery diarrhea.	Most side effects seen with sulfasalazine may occur with any of the other aminosalicylates but much less frequently.
Corticosteroids		
Prednisone	Diabetes mellitus, high blood pressure, cataracts, osteoporosis, thinning of skin, mental problems, acute psychosis, mood swings, infections, acne, excessive body hair (hirsutism), menstrual irregularities, gastritis, peptic ulcer disease.	Diabetes and high blood pressure are more likely to occur in people who have other risk factors.
Budesonide	Diabetes mellitus, high blood pressure, cataracts, osteoporosis (decreased bone density).	Same side effects as prednisone but to a lesser degree.
Immunomodulators		
Azathioprine Mercaptopurine	Anorexia, nausea, vomiting, infection, cancer, allergic reactions, pancreatitis, low white blood cell count, bone marrow suppression, liver dysfunction.	Side effects that are usually dose dependent include bone marrow suppression and liver dysfunction Interval blood monitoring is required.
Cyclosporine	High blood pressure, nausea, vomiting, diarrhea, kidney failure, tremors, infections, seizures, neuropathy, development of lymphomas (cancers of the lymphatic system).	Side effects become more likely with long-term use.
Methotrexate	Nausea, vomiting, abdominal distress, headache, rash, soreness of the mouth, fatigue, scarring of the liver (cirrhosis), low white blood cell count, infections. Causes abortions and birth defects during pregnancy.	Liver toxicity is likely dose dependent Not prescribed for pregnant women.

Drugs	Selected Side Effects	Comments
Infliximab	Infusion reactions, infections, cancer, abdominal pain, liver dysfunction, low white blood cell count.	Infusion reactions are potential immediate side effects that occur during the infusion such as fever, chills, hives, decreased blood pressure, or difficulty breathing. Patients should be screened for tuberculosis before initiating treatment.
Adalimumab	Pain or itching at the injection site, headache, infections, cancer, and hypersensitivity reactions.	Side effect are similar to infliximab except does not cause infusion reactions. Hypersensitive reactions include rash, urticaria, pruritis, and hives.

Table 1. Drugs selected side effects for therapy UC

Antibiotic therapy may induce remission in active CD and UC, although the diverse number of antibiotics tested means the data are difficult to interpret. This systematic review is a
To systematically evaluate the efficacy of antibacterial therapy in ulcerative colitis, Rahimi et al [15] carried out a meta analysis of controlled clinical trials. Within the time period 1966 through September 2006, PUBMED, EMBASE, and SCOPUS were searched for clinical trial studies that investigated the efficacy of antibiotics in ulcerative colitis. These results suggest that adjunctive antibacterial therapy is effective for induction of clinical remission in UC.
Mesalamine is used to treat ulcerative colitis (a condition in which part or all of the lining of the colon [large intestine] is swollen or worn away). Mesalamine delayed-release tablets and controlled-release capsules may be used to treat ulcerative colitis that affects any part of the colon. Mesalamine suppositories and enemas should only be used to treat inflammation of the lower part of the colon. Mesalamine is in a class of medications called anti-inflammatory agents. It works by stopping the body from producing a certain substance that may cause pain or inflammation. Mesalamine (Asacol, Rowasa) and olsalazine (Dipentum) tend to have fewer side effects than sulfasalazine has. The patients with UC take them in tablet form or use them rectally in the form of enemas or suppositories, depending on the area of the colon affected by ulcerative colitis. Mesalamine enemas can relieve signs and symptoms in more than 80 percent of people with ulcerative colitis in the lower left side of their colon and rectum. Olsalazine may cause or worsen existing diarrhea in some people [2-4].
Balsalazide is more effective than mesalazine in induction of remission, but balsalazide has no benefit compared with mesalazine in preventing relapse in the population selected. The number of patients with any adverse events and withdrawals because of severe adverse events is similar for mesalazine and balsalazide [16].
Articles cited were identified *via* a PubMed search, utilizing the words IBD, adherence, compliance, medication and UC. Medication non-adherence is multifactorial involving factors other than dosing frequency. Male gender (OR: 2.06), new patient status (OR: 2.14), work and travel pressures (OR: 4.9) and shorter disease duration (OR: 2.1), among others are

proven predictors of non-adherence in UC. These indicators can identify 'at-risk' patients and allow an individually tailored treatment approach to be introduced that optimizes medication adherence. A collaborative relationship between physician and patient is important. Several strategies for improving adherence have been proven effective including open dialogue that consideration the patient's health beliefs and concerns, providing educational (e.g. verbal/written information, self-management programmes) and behavioural interventions (e.g. calendar blister packs, cues/reminders). Hawthorne *et al* [17] considered that educational and behavioural interventions tailored to individual patients can optimize medication adherence. Additional studies combining educational and behavioural interventions may provide further strategies for improving medication adherence rates in UC. Swaminath *et al* [18] reviews current data to optimize the use of both older and newer drugs in inflammatory bowel disease. For patients with severe UC, steroid dosing has been clarified, and a mega-analysis of steroid outcomes and toxicities has been reported. In regard to mesalamine, recent information has suggested benefit of a higher dose of pH-dependent release mesalamine for patients with moderate UC. Also, a once-daily formulation with multi-matrix system (MMX) technology (Shire Pharmaceuticals, Wayne, PA), has been approved. In regard to cyclosporine, two centers have reported an increased rate of colectomy over a long-duration follow-up of a cyclosporine course given for UC. Additional information regarding thiopurines has been published, including the use of metabolite testing and duration of therapy for these drugs [19, 20].

5-aminosalicylic acids (5-ASAs), a number of oral 5-ASA agents are commercially available, including azo-bond pro-drugs such as sulfasalazine, olsalazine and balsalazide, and delayed- and controlled-release forms of mesalazine [12, 21, 22]. The effectiveness of oral therapy relies on good compliance, which may be adversely affected by frequent daily dosing and a large number of tablets. Furthermore, poor adherence has been shown to be an important barrier to successful management of patients with UC. Recently, new, once-daily formulations of mesalazine including the unique multi-matrix delivery system and mesalazine granules were proven to be efficacious in inducing and maintaining remission in mild-to-moderate UC, with a good safety profile comparable to that of other oral mesalazine formulations. The advantage of low pill burden may contribute to increased long-term compliance and treatment success in clinical practice and might potentially further contribute to a decline in the risk for UC-associated colon cancers. In this systematic review, Lakatos *et al* [19] summarized the available literature on the short- and medium-term efficacy and safety of the new once-daily mesalazine formulations.

5-ASA agents are the first-line therapy for UC. A high-dose, once-daily formulation of 5-ASA known as MMX mesalamine has recently been approved for the treatment of UC. A systematic review of published literature was performed on PubMed using the search terms 'MMX mesalamine' and 'Lialda'. Abstracts presented at US gastroenterology conferences between 2006 and 2007, were also reviewed. MMX mesalamine uses a novel multi-matrix delivery system to achieve a sustained release of 5-ASA throughout the colon. Clinical trials have demonstrated that MMX mesalamine 2.4 g/day or 4.8 g/day is superior to placebo in inducing remission in active mild to moderate UC. The drug is well tolerated with a safety profile comparable to other oral 5-ASAs agents. With a high-dose formulation of 1.2 g 5-ASA per tablet, MMX mesalamine can be administered conveniently at two to four pills once a day. MMX mesalamine is the first and only approved once-daily 5-ASAs treatment option for patients with UC. It is efficacious for the induction of remission in mild to moderate UC and

has a favorable safety profile. With the advantage of low pill burden and easy dosing schedule, it may potentially improve patient compliance and treatment success [20].

The efficacy of 5-ASAs in ulcerative colitis (UC) has been studied previously in meta-analyses. However, several randomized controlled trials (RCTs) have been published recently, and no previous meta-analysis has studied the effect of 5-ASA dosage used. Ford *et al* [23] suggested that 5-ASAs are highly effective for inducing remission and preventing relapse in UC. Evidence suggests that 5-ASA doses of ≥2.0 g/day have greater efficacy, although doses >2.5 g/day do not appear to lead to higher remission rates.

Sulfasalazine (SSZ) does not differ from mesalamine or olsalazine in terms of efficacy and tolerability in UC. Withdrawal from study due to adverse events was significantly lower for balsalazide compared with SSZ. Convincing conclusions on the comparison of effectiveness and safety of balsalazide and SSZ in UC remains to be elucidated by further clinical trials. Considering the lower cost of treatment with SSZ and the equal rate of adverse events with other 5-ASAa, it is not surprising to suggest SSZ as a first-choice treatment for UC and reserve 5-ASAs for when SSZ intolerability occurs [24].

Ulcerative proctitis (UP) is a common presentation of UC. Extensive Medline/Embase literature search was performed to identify relevant articles. Topical medication with rectally administered 5-ASA/corticosteroid suppositories or enemas is an effective treatment for most UP patients. Locally administered 5-ASA is more efficacious than oral compounds. The combination of topical 5-ASA and oral 5-ASA or topical steroids should be considered for escalation of treatment. Maintenance treatment is indicated in all UC cases. 5-ASA suppositories are suggested as first-line maintenance therapy if accepted by patients, although oral 5-ASA as maintenance therapy might prevent proximal extension of the disease. After re-assessment, chronically active patients refractory or intolerant to 5-ASAs and corticosteroids may require immunomodulators or biological therapy [12, 20-23]. Rectal 5-ASA should be considered a first-line therapy for patients with mild to moderately active distal UC. The optimal total daily dose and dose frequency of 5-ASA remain to be determined. Future research should define differences in efficacy among patient subgroups defined by proximal disease margin and disease activity. There is a strong need for consensus standardization of outcome measurements for clinical trials in ulcerative colitis [25]..

Infliximab is effective for treatment of moderate-to-severe UC and is recommended for patients who have had an inadequate response to medical therapy or who are intolerant of or do not desire to take the potential risk of using specific agents including immunomodulators (cyclosporine A, azathioprine, or 6-mercaptopurine), corticosteroids, and, potentially, mesalamine. Future trials are needed to assess the efficacy of infliximab with immunomodulators to see if additional benefit is achieved so that the risk-benefit ratio is positive. Based on the favorable efficacy of infliximab for UC therapy, the ground work has been established for evaluating infliximab and addressing some of the many unanswered questions and also for assessing other anti-TNF agents and streamlining the anti-TNG antibody to improve efficacy, reduce side effects, and ease administration [22]. Infliximab (Remicade) is specifically for adults and children with moderate to severe ulcerative colitis who don't respond to or can't tolerate other treatments. The drug has been linked to an increased risk of infection, especially tuberculosis, and may increase your risk of blood problems and cancer. Before taking infliximab a skin test for tuberculosis and a chest X-ray are necessary if the patients lived or traveled extensively where tuberculosis has been found. Also, because Remicade contains mouse protein, it can cause serious allergic reactions in some people — reactions that may be delayed for days to weeks after starting

treatment. Once started, infliximab is often continued as long-term therapy, although its effectiveness may wear off over time.

2.2 Corticosteroids

Corticosteroids can help reduce inflammation, but they have numerous side effects, including a puffy face, excessive facial hair, night sweats, insomnia and hyperactivity. Long-term use of these drugs in children can lead to stunted growth. Also, corticosteroids don't work for everyone who has ulcerative colitis. Doctors generally use corticosteroids only if you have moderate to severe inflammatory bowel disease that doesn't respond to other treatments. Corticosteroids aren't for long-term use and are generally prescribed for a period of three to four months. They may also be used in conjunction with other medications as a means to induce remission. These, too, are only for short-term use [2, 8].

MEDLINE, EMBASE, and the Cochrane central register of controlled trials were searched (through December 2010) by Ford *et al* [26]. Randomized controlled trials (RCTs) recruiting adults with active or quiescent CD comparing standard glucocorticosteroids or budesonide with placebo or each other, or comparing standard glucocorticosteroids with placebo in active UC, were eligible. Dichotomous data were extracted to obtain relative risk (RR) of failure to achieve remission in active disease, and RR of relapse of activity in quiescent disease, with a 95% confidence interval (CI). Adverse events data were extracted where reported. Standard glucocorticosteroids are probably effective in inducing 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.

Recent progress in both basic and clinical research has led us to develop sophisticated and effective medical therapy of UC. Although classical agents such as aminosalicylates, corticosteroids and immunomodulatory drugs have remained as the gold standard for decades, their novel formulations and/or dosage regimens have changed their placements in the medical management of UC. In addition, studies have shown that a number of novel therapeutic agents, designed to target specific mechanisms involved in the inflammatory cascade, have efficacy for the treatment of UC and they will have significant clinical impacts in the near future. A clear understanding of the proven and potential benefits of both the standard and emerging therapies will be required for the optimum individual care of patients with varied clinical presentations [12, 18, 27-29].

2.3 Immune system suppressors

These drugs also reduce inflammation, but they target the immune system rather than inflammation itself. Because immune suppressors can be effective in treating ulcerative colitis, scientists theorize that damage of the digestive tissues is caused by the body's immune response to an invading virus or bacterium or even to patients own tissue. By suppressing this response, inflammation is also reduced. Azathioprine (Imuran) and mercaptopurine (Purinethol) have been used to treat CD and UC for years, but their role in ulcerative colitis is only now being studied. Because azathioprine and mercaptopurine act slowly, they're sometimes initially combined with a corticosteroid, but in time, they seem to produce benefits on their own, with less long-term toxicity. Side effects can include allergic reactions, bone marrow suppression, infections, and inflammation of the liver and pancreas. If a patient is taking either of these medications, he or she'll need to follow up closely with his or her doctor and have your blood checked regularly to look for side effects.

Cyclosporine (Neoral, Sandimmune), a potent drug, is normally reserved for people who don't respond well to other medications or who face surgery because of severe UC.

Published trials evaluating the efficacy of 6-thioguanine anti-metabolites in the treatment of UC have yielded conflicting results. Leung *et al* [30] performed a systematic review and meta-analysis to evaluate the clinical efficacy of 6-thioguanine anti-metabolites for the maintenance of clinical remission after standard induction with corticosteroids. A comprehensive search of online databases was conducted. Only randomized controlled trials with 6-thioguanine antimetabolites within a minimum duration of follow-up of 6 months were selected. Five trials were included in the meta-analysis. Pooled results demonstrated a modest efficacy of azathioprine (AZA) for the treatment of ulcerative colitis. However, the use of AZA for the management of UC is not based on high-quality evidence.

There remains controversy regarding the efficacy of thiopurine analogs (AZA and 6-MP), methotrexate (MTX), and cyclosporine for the treatment of inflammatory bowel disease (IBD). An updated systematic review of the literature to clarify the efficacy of immunosuppressive therapy at inducing remission and preventing relapse in UC and CD was performed. Most evidence relates to AZA/6-MP where there is no statistically significant benefit at inducing remission in active CD and UC. Thiopurine analogs may prevent relapse in quiescent UC and CD. However, there is a paucity of data for immunosuppressive therapy in IBD and more research is needed [31].

Over the last decade, the increasing knowledge on the pathogenic mechanisms underlying intestinal inflammation has led to the development of a number of biological agents, mainly addressed to molecules and/or pathways demonstrated to have a pathogenic role in UC. In UC, clinical course and therapeutic decisions mainly depend on disease activity and extent. While therapeutic approach to mild-to-moderate UC by using aminosalicylates and corticosteroids has been well established, treatment of severe UC is far from being satisfactory. A severe attack of UC remains a challenge to be managed jointly by gastroenterology, surgery, and intensive care units. However, the recent introduction of biological therapies has led to promising changes in the management of UC patients. Aim of this paper is to review the recent advances and future perspectives for the use of biological agents in UC [32, 33]. Side effects of cyclosporine include high blood pressure, renal function impairment, and tingling sensations in the extremities. More serous side effects include anaphylactic shock and seizures.

Mucosal macrophages play an important role in the mucosal immune system, and an increase in the number of newly recruited monocytes and activated macrophages has been noted in the inflamed gut of patients with IBD. Activated macrophages are thought to be major contributors to the production of inflammatory cytokines in the gut, and imbalance of cytokines is contributing to the pathogenesis of IBD. The intestinal inflammation in IBD is controlled by a complex interplay of innate and adaptive immune mechanisms. Cytokines play a key role in IBD that determine T cell differentiation of Th1, Th2, T regulatory and newly described Th17 cells. Cytokines levels in time and space orchestrate the development, recurrence and exacerbation of the inflammatory process in IBD [34-36].

Progress has occurred in all major areas relevant to IBD pathogenesis, which include the external environment, genetics, microbial factors, and the immune system. This review presents an update on the specific major advances that have occurred in each of these four areas, briefly discusses the therapeutic implications of the observed progress, and points out the additional work that needs to be accomplished in the next few years to reach a full understanding of IBD etiopathogenesis [35,36].

VSL#3 (VSL#3) is a high-concentration probiotic preparation of eight live freeze-dried bacterial species that are normal components of the human gastrointestinal microflora, including four strains of lactobacilli (*Lactobacillus casei, L. plantarum, L. acidophilus,* and *L. delbrueckii* subsp. *bulgaricus*), three strains of bifidobacteria, and *Streptococcus salivarius* subsp. thermophilus. Data from noncomparative trials suggest that VSL#3 has clinical potential in the treatment of active mild to moderate ulcerative colitis and as maintenance therapy for patients with ulcerative colitis in remission. In addition, a randomized, open-labelled, multicenter trial showed that VSL#3 in combination with low-dose balsalazide (a prodrug of mesalazine [mesalamine; 5-ASA]) was more effective than standard doses of basalazide or mesalazine monotherapy in the treatment of acute mild to moderate ulcerative colitis. Randomized, double-blind, placebo-controlled studies have shown that VSL#3 is effective in preventing the onset of acute pouchitis in patients with newly formed surgical pouches, and in maintaining remission following antibacterial treatment of acute pouchitis in patients with a history of refractory or recurrent pouchitis. Treatment guidelines from the US and the UK include VSL#3 as a therapeutic option for the prevention of pouchitis relapse in patients with chronic pouchitis. In general, VSL#3 was well tolerated in clinical trials. Large, well designed, controlled confirmatory clinical trials will further determine the place of VSL#3 in the treatment of UC [18].

2.4 Nicotine

The skin patches seem to provide short-term relief from flare-ups of UC for some people, especially people who formerly smoked. How nicotine patches work isn't exactly clear, and the evidence that they provide relief is contested among researchers.

UC is characterized by impairment of the epithelial barrier and the formation of ulcer-type lesions, which result in local leaks and generalized alterations of mucosal tight junctions. Ultimately, this results in increased basal permeability. Although disruption of the epithelial barrier in the gut is a hallmark of inflammatory bowel disease and intestinal infections, it remains unclear whether barrier breakdown is an initiating event of UC or rather a consequence of an underlying inflammation, evidenced by increased production of proinflammatory cytokines. UC is less common in smokers, suggesting that the nicotine in cigarettes may ameliorate disease severity. The mechanism behind this therapeutic effect is still not fully understood, and indeed it remains unclear if nicotine is the true protective agent in cigarettes. Nicotine is metabolized in the body into a variety of metabolites and can also be degraded to form various breakdown products. Possibly, these metabolites or degradation products may be the true protective or curative agents. A greater understanding of the pharmacodynamics and kinetics of nicotine in relation to the immune system and enhanced knowledge of gut permeability defects in UC are required to establish the exact protective nature of nicotine and its metabolites in UC. This review suggests possible hypotheses for the protective mechanism of nicotine in UC, highlight the relationship between gut permeability and inflammation, and indicates where in the pathogenesis of the disease nicotine may mediate its effect [1-3, 12-14].

UC is predominantly a disease of non-smokers, and nicotine may be the agent responsible for this association. Transdermal nicotine has been shown to improve disease activity and sigmoidoscopic appearance in the active disease, but in one study it had no effect on maintenance of remission. Since side-effects with nicotine patches occur in up to two thirds of patients, attempts to reduce systemic levels and improve drug tolerance have been developed with colonic delivery systems of nicotine. Preliminary observations with nicotine

enemas in UC have shown clinical benefit, but controlled trials are needed. Mechanisms responsible for the association of smoking with colitis and for the therapeutic effect of nicotine remain an enigma; possibilities include: modulation of the immune response, alterations of colonic mucus and eicosanoid production, changes in rectal blood flow, decreased intestinal permeability and the release of endogenous glucocorticoids [19-22].

Smoking has been associated with a decreased frequency of UC. Currently, the role of nicotine for the treatment of UC is not established. Several studies have evaluated nicotine gum and transdermal patches as supplemental therapy for stable UC, but nicotine has not been compared with other treatment modalities. Nicotine dosages in the studies have varied from 5 to 30 mg/d without apparent dose-related therapeutic effects, and many patients have found relief from placebo treatment. Patients often do not tolerate nicotine therapy's adverse effects, such as nausea, light-headedness, and headache. Due to the cyclic disease course of UC and the potential addictiveness of nicotine, further large studies are warranted to assess the benefits of nicotine therapy for UC [29].

There are significant proportions of patients with UC who experience adverse effects with current therapies. Consequently, new alternatives for the treatment of UC are constantly being sought. Probiotics are live microbial feed supplements that may beneficially affect the host by improving intestinal microbial balance, enhancing gut barrier function and improving local immune response. Mallon *et al* [12] assessed the efficacy of probiotics compared with placebo or standard medical treatment (5-aminosalicylates, sulfasalazine or corticosteroids) for the induction of remission in active ulcerative colitis. A comprehensive search for relevant randomised controlled trials (RCT's) was carried out using MEDLINE (1966-January 2006), EMBASE (January 1985- 2006) and CENTRAL. The Cochrane IBD/FBD Review Group Specialised Trials Registrar was also searched. The Australasian Medical Index, Chinese Biomedical Literature Database, Latin American Caribbean Health Sciences Literature (LILACS), and the Japan Information Centre of Science and Technology File on Science, Technology and Medicine (JICST-E) were also used to identify abstracts. Conference proceedings from the Falk Symposium, Digestive Disease Week (DDW) and the United European Digestive Disease week were hand-searched. Authors of relevant studies and drug companies were contacted regarding ongoing or unpublished trials that may be relevant to the review. However, there is limited evidence that probiotics added to standard therapy may provide modest benefits in terms of reduction of disease activity in patients with mild to moderately severe UC. Whether probiotics are as effective in patients with severe and more extensive disease and whether they can be used as an alternative to existing therapies is unknown [12].

2.5 Heparin

Heparin is a naturally-occurring anticoagulant produced by basophils and mast cells. Heparin acts as an anticoagulant, preventing the formation of clots and extension of existing clots within the blood. While heparin does not break down clots that have already formed (unlike tissue plasminogen activator), it allows the body's natural clot lysis mechanisms to work normally to break down clots that have formed.

An increased risk of thrombosis in UC coupled with an observation that UC patients being treated with anticoagulant therapy for thrombotic events had an improvement in their bowel symptoms led to trials examining the use of unfractionated heparin (UFH) and low molecular weight heparins (LMWH) in patients with active UC. There is evidence to suggest that LMWH may be effective for the treatment of active UC. When administered by

extended colon-release tablets, LMWH was more effective than placebo for treating outpatients with mild to moderate disease. This benefit needs to be confirmed by further randomized controlled studies. The same benefits were not seen when LMWH was administered subcutaneously at lower doses. There is no evidence to support the use of UFH for the treatment of active UC. A further trial of UFH in patients with mild disease may also be justified. Any benefit found would need to be weighed against a possible increased risk of rectal bleeding in patients with active UC [37].

2.6 Interferons

Interferons (IFNs) are cytokines which possess immunoregulatory properties and have been used to successfully treat a number of chronic inflammatory disorders. It has been postulated that Type I IFNs may be able to re-establish the Th1/Th2 balance in Th2 predominant diseases like ulcerative colitis.

Seow *et al* [38] reported that four studies were eligible for inclusion. Three studies compared type I IFNs to placebo and a single study compared IFNs to prednisolone enemas in patients with left-sided colitis. Meta-analysis was based on the three IFN-placebo studies. There was no significant benefit of type I IFNs over placebo for inducing remission in ulcerative colitis (RR 1.24; 95% CI 0.81 to 1.90). There were no statistically significant differences in any of the secondary outcome variables. Conclusions were suggested by Seow *et al* [38] that the existing literature does not support the efficacy of type I IFNs for induction of remission in patients with UC. Given concerns regarding the tolerability of IFN therapy, we suggest that the results of two ongoing trials are evaluated for efficacy and safety prior to development or commencement of further randomised controlled trials of type I IFNs in UC.

3. Treatment of traditional Chinese medicine

Traditional Chinese medicine (TCM) believes that the major pathologies of UC include spleen and stomach dysfunctions, intestinal turbid accumulations, and blood and qi disturbances. Therefore, TCM treatment strategies are to restore organ functioning, eliminate turbid accumulations and harmonize the flows of qi and blood. In clinical applications, if individuals have obvious pus, mucus or bloody loose bowels, physicians will focus on clearing pathogens like damp-heat or damp-cold, so as to improve the bowel environment. Afterwards, notifying methods are employed to overcome the internal weakness and promote a longer remission period [2, 39-42].

Chinese medicine is getting more and more popular nowadays in the whole world for improving health condition of human beings as well as preventing and healing diseases. Chinese medicine is a multi-component system with components mostly unknown, and only a few compounds are responsible for the pharmaceutical and/or toxic effects. The large numbers of other components in the Chinese medicine make the screening and analysis of the bioactive components extremely difficult. So, separation and analysis of the desired chemical components in Chinese medicine are very important subjects for modernization research of Chinese medicine. Thus, many novel separation techniques with significant advantages over conventional methods were introduced and applied for separation and analysis of the chemical constituents in Chinese medicine. This review presents just a brief outline of the applications of different separation methods for the isolation and analysis of Chinese medicine constituents [2, 7]. Chinese medicine was widely used in the treatment of

UC. Treatment of chronic UC by traditional Chinese and Western medicine is safe and effective in maintaining remission [39, 40].

Stimulation of acupuncture not only enhances the immune modulation effect, but also mobilizes the innate healing power inside the body. For the localized problems like inflammation, ulcers, muscular spasms and sluggish flow, acupuncture and moxibustion are particularly effective and thus facilitate structural recovery [41, 42]. Major points are navel's four-point (one-thumb-width apart from the navel, located in three, six, nine & twelve o'clock), *tian-shu, guan-yuan* & *qi-hai*; Assist points are *da-chang-shu, zhang-qiang, pi-shu, wei-shu, zu-san-li* & *san-yin-jiao.* When applying, firstly the four-point needle should be punctured in 0.3-0.5 cm deep 30-second for about rotations, with stimulation of the four locations in a clockwise sequence, without needle retention. Then one more major point and 2 to 3 assist points should be selected for stimulation, with the needles retaining on the locations for 15-20 minutes, and the moxa cones can be attached for heating during this time. Procedure is performed once daily or every two days with ten times is one course [2, 42].

Moxibustion can also be used to boost the weakened systems, particularly for individuals with chronic symptoms. Below are suggested protocols. The major points are *zhong-wan, tian-shu, guan-yuan* & *shang-ju-xu, and the* assist points are *pi-shu, shen-shu, da-chang-shu, zu-san-li, tai-xi, tai-chong, san-yin-jiao* & *zhong-iv-shu*. Each time, 1-2 major points should be selected with heat for 30-40 minutes, while 2-3 assist points should be punctured with heat for 15-20 minutes. This procedure is performed once daily or every two days, with 15-20 times in one course.

Acupuncture-type treatments are among the most popular options. Several studies have reported that moxibustion is effective in ulcerative colitis (UC). The objective of this review was to assess the clinical evidence for or against moxibustion as a treatment for UC. Lee *et al* [43] searched the literature using 18 databases from their inception to February 10, 2010, without language restrictions. Randomized clinical trials (RCTs) were included, in which human patients with UC were treated with moxibustion. Studies were included if they were placebo-controlled or controlled against a drug therapy or no treatment group. The methodological quality of all RCTs was assessed using the Cochrane risk of bias. In total, five RCTs were included. All were of low methodological quality. They compared the effects of moxibustion with conventional drug therapy. Three tested moxibustion against sulfasalazine and two against sulfasalazine plus other drugs. A meta-analysis of five RCTs showed favorable effects of moxibustion on the response rate compared to conventional drug therapy (n = 407; risk ratio = 1.24, 95% CI = 1.11 to 1.38; $P < 0.0001$; heterogeneity: $I2 = 16\%$). The results showed that current evidence is insufficient to show that moxibustion is an effective treatment of UC. Most of included trials had high risk of bias. More rigorous studies seem warranted.

In addition to controlling inflammation, some medications may help relieve the signs and symptoms. Depending on the severity of UC, the patients are recommended one or more of the following [2, 8, 18-21].

Antidiarrheals: A fiber supplement such as psyllium powder (Metamucil) or methylcellulose (Citrucel) can help relieve signs and symptoms of mild to moderate diarrhea by adding bulk to the stool. For more severe diarrhea, loperamide (Imodium) may be effective. Use anti-diarrheal medications with great caution, however, because they increase the risk of toxic megacolon.

Laxatives: In some cases, swelling may cause the intestines to narrow, leading to constipation.

Pain relievers: For mild pain, the patients recommend acetaminophen (Tylenol, others). Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be applied such as aspirin, ibuprofen (Advil, Motrin, others) or naproxen (Aleve). These are likely to make patient's symptoms worse.
Iron supplements: If patients have chronic intestinal bleeding, they may develop iron deficiency anemia. Taking iron supplements may help restore patient's iron levels to normal and reduce this type of anemia once the bleeding has stopped or diminished.
Parenteral hyperalimentation: For severe UC patients, it is one kind of security, the effective feasible method.

4. Surgery

Surgery is required in the vast majority of patients with CD and in approximately one-third of patients with UC. Similar to medical treatments for IBD, significant advances have occurred in surgery. Advances in CD include an emphasis upon conservatism as exemplified by more limited resections, strictureplasties, and laparoscopic resections. The use of probiotics in selected patients has improved the outcome in patients with pouchitis following restorative proctocolectomy for UC. It is anticipated that ongoing discoveries in the molecular basis of IBD will in turn identify those patients who will best respond to surgery [44]. Emergency surgery may be necessary for acute life-threatening attacks with massive bleeding, perforations, toxic megacolon, or blood clotting. Since the introduction of laparoscopy into colorectal surgery in the early 1990s, almost every procedure was attempted laparoscopically. Consequently, many very experienced surgical groups conducted numerous trials in an attempt to determine whether laparoscopy in IBD is indeed beneficial or not. The focus of this review is minimally invasive procedures in patients with UC [45].

5. Summary

Ulcerative colitis (UC) and Crohn's disease (CD) are two primary types of inflammatory bowel disease (IBD). UC is an inflammatory destructive disease of the large intestine occurred usually in the rectum and lower part of the colon as well as the entire colon. Drug therapy is a main choice for UC treatment and medical management should be as a comprehensive one. Several types of medications are used to control the inflammation or reduce symptoms caused by ulcerative colitis. The treatment of UC depends on its severity, location and the presence of complications, so drug therapies must be custom-designed for each patient. Findings which medications best alleviate the symptoms may take time. The goal of medical treatment is to reduce the inflammation that triggers the signs and symptoms [2-4]. In the best cases, this may lead not only to symptom relief but also to long-term remission. Azulfidine, Asacol, Pentasa, Dipentum, and Rowasa all contain 5-ASA, which is the topical anti-inflammatory ingredient. In UC patients with moderate to severe disease and in patients who failed to respond to 5-ASA compounds, systemic corticosteroids should be used. To minimize side effects, corticosteroids should be gradually reduced as soon as the disease remission is achieved [13-15]. Surgery or immunomodulator is considered for patients with corticosteroid-dependent or unresponsive to corticosteroid treatment. Immunomodulators used for treating severe UC include azathioprine/6-MP, methotrexate, and cyclosporine [46-50]. Integrated traditional Chinese and Western medicine is safe and effective in maintaining remission in patients with UC.

The goal of drug therapy is to induce and maintain remission, and to improve the quality of life for people with ulcerative colitis. Several types of drugs are available. Drug treatment ulcerative colitis includes the following three categories: aminosalicylates, corticosteroids and immunomodulators. Other drugs may be given to relax the patient or to relieve pain, diarrhea, or infection.

5.1 Aminosalicylates

These drugs that contain 5-aminosalicyclic acid (5-ASA) help control inflammation. Sulfasalazine is a combination of sulfapyridine and 5-ASA. The sulfapyridine component carries the anti-inflammatory 5-ASA to the intestine. However, sulfapyridine may lead to side effects such as nausea, vomiting, heartburn, diarrhea, and headache. Other 5-ASA agents, such as olsalazine, mesalamine, and balsalazide, have a different carrier, fewer side effects, and may be used by people who cannot take sulfasalazine. 5-ASAs are given orally, through an enema, or in a suppository, depending on the location of the inflammation in the colon. Most people with mild or moderate ulcerative colitis are treated with this group of drugs first. This class of drugs is also used in cases of relapse.

5.2 Corticosteroids

Corticosteroids such as prednisone, methylprednisone, and hydrocortisone also reduce inflammation. They may be used by patients who have moderate to severe UC or who do not respond to 5-ASA drugs. Corticosteroids, also known as steroids, can be given orally, intravenously, through an enema, or in a suppository, depending on the location of the inflammation. The drugs can cause side effects such as weight gain, acne, facial hair, hypertension, diabetes, mood swings, bone mass loss, and an increased risk of infection. For this reason, they are not recommended for long-term use, although they are considered very effective when prescribed for short-term use.

5.3 Immunomodulators

These drugs such as azathioprine and 6-mercapto-purine (6-MP) reduce inflammation by affecting the immune system. Azathioprine and 6-MP are used for patients who have not responded to 5-ASAs or corticosteroids or who are dependent on corticosteroids. Immunomodulators are administered orally, however, patients are slow-acting and it may take up to 6 months before the full benefit. Patients taking these drugs are monitored for complications including pancreatitis, hepatitis, a reduced white blood cell count, and an increased risk of infection. Cyclosporine A may be used with 6-MP or azathioprine to treat active, severe UC in patients who do not respond to intravenous corticosteroids.

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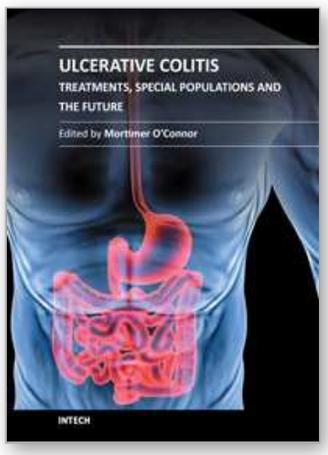

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This book is intended to act as an up to date reference point and knowledge developer for all readers interested in the area of gastroenterology and in particular Ulcerative Colitis. All of the chapter authors are experts in their fields of publication and deserve individual credit and praise for their contributions to the world of Ulcerative Colitis. We hope that you will find this publication informative, stimulating and a reference point for the area of Ulcerative colitis as we move forward in our understanding of the field of medicine.

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