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Princy L Palatty
Department of Pharmacology,
Father Muller Medical College,
Kankanady, Mangalore,
Karnataka, India

Suresh Rao
Department of Research in
Radiation Oncology,
Mangalore Institute of
Oncology, Pumpwell,
Mangalore, India

Mohammed Adnan
MBBS Student, Father Muller
Medical College, Kankanady,
Mangalore, Karnataka, India

Taresh S Naik
MBBS Student, Father Muller
Medical College, Kankanady,
Mangalore, Karnataka, India

Michael LJ Pais
MBBS Student, Father Muller
Medical College, Kankanady,
Mangalore, Karnataka, India

Avinash K Kudva
Department of Biochemistry,
Mangalore University,
Mangalagangothri, Mangalore,
Karnataka, India

Manjeshwar Shrinath Baliga
Department of Research in
Radiation Oncology,
Mangalore Institute of
Oncology, Pumpwell,
Mangalore, India

Correspondence
Manjeshwar Shrinath Baliga
Department of Research in
Radiation Oncology,
Mangalore Institute of
Oncology, Pumpwell,
Mangalore, India

Unraveling of ulcerative colitis and its therapy: A review

Princy L Palatty, Suresh Rao, Mohammed Adnan, Taresh S Naik, Michael LJ Pais, Avinash K Kudva and Manjeshwar Shrinath Baliga

Abstract

Ulcerative colitis is a chronic remitting inflammatory disorder of the colon involving only the mucosa and the sub mucosa. Though a disease of the developed world, recent years have seen an increase in the developing world as well. Lifestyle changes have been attributed to this current trend. However the role of genetic factors cannot be ruled out, as India heads the list with the North Indian population having prevalence almost equal to that of the Caucasians. While the exact etiopathogenesis of Ulcerative colitis still remains vague, it has been well accepted that it is a continuous inflammatory response in genetically predisposed individuals to environmental stimuli especially intraluminal antigens resulting in tissue damage. Among these factors, smoking and appendicectomy are known to play a protective role. The immunological response is a T helper 2 cell response with a possible involvement of oxidative stress. The mucosa and sub mucosa become infiltrated with acute and chronic inflammatory cells with release of various inflammatory cytokines. Erythematous and friable mucosa with pseudo polyps are a characteristic feature of ulcerative colitis. It can present with intestinal manifestations as well as with extra intestinal involvement of joints, liver, pancreas, eyes or skin. Clinically, gastrointestinal symptoms like diarrhoea, obstipation and weight loss are seen. Aminosalicylates, corticosteroids and immunosuppressants remain the mainstay of treatment for this disease. The medical treatment involves a stage of inducing remission and then maintaining this remission with the help of various drugs. Surgery is indicated in a few cases. However with better understanding of the pathology, newer drugs like anti TNF α , monoclonal antibodies, PPAR γ ligand, epidermal growth factor, transdermal nicotine, short chain fatty acids and probiotics have come into the picture. Further studies and clinical trials regarding these drugs have to be done; nevertheless they hold a bright future in the management of ulcerative colitis.

Keywords: Ulcerative Colitis, Th2 response, Aminosalicylates, Rosiglitazone maleate, Anti TNF α treatment

Introduction

Ulcerative colitis, a chronic inflammatory disease of the colon, has had a severe toll on the health economy all over the world due its increasing incidence. A disease of the developed world, ulcerative colitis is becoming more common in the developing world with improvement in the standard of living and change of lifestyle. It comes under the category of inflammatory bowel diseases (IBD) which includes Crohn's disease as well. In fact, it has also been proposed that ulcerative colitis and Crohn's disease, though generally accepted as clinically distinct conditions with distinguishing clinical, anatomical and histological findings, are not two separate entities but represent a continuum of diseases [1].

Ulcerative colitis pursues a protracted relapsing and remitting course, usually extending over a period of several years and primarily involves only the mucosa and sub mucosa of the colon. Extent of involvement can range from the distal rectum to the entire colon. In adults, 55% present with proctitis, 30% with left sided colitis and 15% with pancolitis [2]. It has a serious effect on the quality of life of the patient with its intestinal and extra intestinal manifestations, and moreover the available therapies are mostly inadequate or toxic [3]. Though the exact etiology of this inflammatory condition is still not known, a number of theories have been proposed which have gone a long way in the evolution of new and novel means for the treatment of this disease [4].

Ulcerative colitis (UC), Crohn's disease (CD), regional enteritis and Irritable Bowel Syndrome (IBS) are terms which are often wrongly interchanged due to their similar presentations and unknown etiology. Each of them has their own distinct meaning and it is imperative to differentiate between them. UC is a chronic recurrent ulceration of the colon chiefly involving the mucosa and sub mucosa. On other hand, Crohn's disease or regional enteritis can involve any part of the gastrointestinal tract and that too transmurally leading to fistulas, strictures and perforations. While the above two were inflammatory conditions, IBS is a non-inflammatory condition with no pathological basis and has more of a psycho physiologic basis.

Incidence and Epidemiology

Ulcerative colitis, a disease predominantly of the developed countries and higher socioeconomic groups, has a bimodal distribution with a first peak in 15 to 30 years of age and a second smaller peak in the age group of 50 to 70 years. However no age has been found immune to the disease [1]. There is disagreement in the sex distribution as some studies claim an equal distribution while others observes a slight male predominance [1, 5]. Though worldwide in distribution, the incidence of the disease appears to vary with geographic location and race. It is found to be more common in the Caucasians and Ashkenazic Jewish origin as compared to other backgrounds [1]. Higher rates are also found in the more developed countries of Scandinavia, Northern Europe and North America, with lower rates in Asia, Africa and Europe. This point towards a conclusion of gradually increasing risk as one moves further away from the equator [4]. On the contrary, over the past few years an increasing incidence has been recorded in the Asians and African Americans with a 10 fold increase in Seoul, Korea. The worldwide prevalence rate ranges from 5.5 to 243 per 100,000 populations [6]. In Western Europe and in the USA, UC has an incidence of approximately 6 to 8 cases per 100,000 populations and an estimated prevalence of approximately 70 to 150 per 100,000 populations [5].

Ulcerative Colitis in India

The rising rate of Ulcerative colitis in the developing world has substantially affected India as well. In India, the incidence is 6.02 per 100,000 population and the prevalence 44.3 per 100,000 population [7]. South Asians who have migrated to developed countries have shown an increased risk of developing IBD. This emphasizes the importance of environment and lifestyle in the development of this disease [4]. However, the role of genetic factors cannot be ruled out. While there was an increase in incidence of UC and a much lower rise in CD in Asia, a substantial variation in the incidence among the different ethnic groups was noted. The highest rates were recorded from India, Japan and the Middle East and a genetic predisposition in the South Asians (Indians, Pakistanis and Bangladeshis) to UC was also observed [8]. In fact among the various Asian countries, India probably heads the list [7].

The clinical phenotypes and complications in the Asian population are similar to that in the Caucasians with a little heterogeneity among the different Asian populations [8]. In studies done in Malaysia, it was observed that Indians residing in South East Asia have a higher incidence of IBD compared to the Chinese and Malays [6]. They also tend to have an extensive disease with extra intestinal

manifestations [9]. Another study conducted in UK revealed that the Asians (Indians, Pakistanis) have increased chances of developing IBD compared to the indigenous European population [10]. This goes in favour of a genetic predisposition when the environmental factors are nullified. Even in the Indian population, a higher incidence is seen among the North Indians as compared to those living further down. The incidence in North India has found to be not much less than that in North America and Europe [11]. Studies have even shown that the common SNPS in the MDR1 gene seen in the Caucasian population are seen in the North Indian population as well [12].

Etiology

The exact etiopathogenesis of ulcerative colitis is still under study but is thought to be multifactorial. It is presently accepted that ulcerative colitis is a continuous inflammatory response in genetically predisposed individuals to environmental stimuli especially intraluminal antigens resulting in tissue damage.

Genetic

Though a genetic background has been postulated for ulcerative colitis (UC), this association is not as evident as in Crohn's disease (CD). This is based on the presence of an increased incidence of IBD among first degree and second degree relatives and a relative higher risk among siblings [1]. It was observed that in families with a high incidence of IBD among first degree relatives, 75% of the affected are concordant with either UC or CD while the remaining 25% are not concordant. This goes in favour of a complex overlapping multigenetic inheritance trait in contrast to the traditional Mendelian inheritance. Further support for a genetic susceptibility comes from the observation of association between IBD and other syndromes with a genetic predisposition [1]. However, the concordance rate for monozygotic and dizygotic twins ranges from 6% to 17% and 0% to 5% respectively, which is almost on par with that of non twin siblings [1].

In recent years, much importance has been given to genetic heterogeneity, a situation in which any number of genetic causes can act independently to produce an identical disease phenotype, in IBDs [13]. The main areas of linkage being studied in relation to IBDs are chromosome 16 (IBD1), 12 (IBD3), 6 (IBD3- the HLA region), and 14 [2]. Genome wide association studies have shown a linkage between UC and regions of chromosome 3, 7 and 12 [5]. Studies have also shown that an association exists between genes of the HLA region, involved in regulating the immune response, and ulcerative colitis. This association was observed to be strongest in patients with extensive colitis. A positive association with DR2 (in particular, DRB1*1502 subtype) and the rare alleles DRB1*0103 and DRB1*12, and a negative association with DR4 and Drw6 have been reported [5]. DRB1*0103 has more often been associated with extensive and severe colitis or extra intestinal manifestations [13].

Studies have shown that mutations in the genes located on IBD1 locus on chromosome 16, coding for a protein NOD-2 (nucleotide binding oligomerization domain 2 or CARD-15 – caspase activating recruitment domain), have association with IBDs more so with CD than UC. This protein activates NF-kappaB by responding to bacterial lipopolysaccharides and was the first gene to be clearly associated with IBD [1, 2].

Geary *et al.* in their studies suggested an increased risk of having UC and developing extra intestinal manifestations with the presence of 1 *NOD2* mutation [14]. Variants of the *IL-23R*, *IL-12B*, and *STAT3* genes have been associated specifically with UC [15].

In addition, polymorphisms of *IL-1* receptor antagonist might be linked to the severity and extent of disease, particularly in patients positive for *pANCA* and *MUC3* [5]. Several lines of evidence suggest a role for multidrug resistance gene (*MDR1*) and its product P-glycoprotein 170 in the pathogenesis of IBD. In particular, *ABCB1/MDR1* seems to determine susceptibility and phenotype for UC [13]. At the same time an Italian study states that *MDR1* polymorphisms have no significant role to play in the susceptibility to IBD and the response to treatment [16]. It was also suggested that polymorphisms in the *Meprin* – gene *MEP1A* may be significantly associated with UC [13]. *TL1A (TNFSF15)*, an IBD-associated gene, is a central immune regulator in IBD and a member of the *TNF* super family. *TL1A* and *DR3* expression is increased on T cells and macrophages in the mucosa of patients with IBD. *TL1A* is the only gene that has been associated with both Asian and Caucasian IBD. Haplotypes A and B are associated with IBD susceptibility in non-Jewish Caucasian CD and UC [15].

Environment

bacterial components in the intestine and form antigenic particles, which can also act as triggers for IBDs [3].

Stress and smoking have also a significant role to play in precipitation of attacks of IBD [4]. It is the long term stress that appears to increase the risk of flare ups of the disease. About 40% of patients with UC have reported stress to be a potential trigger [5]. On the contrary, cigarette smoking appears to play a protective role against flare ups of UC [4]. This protective action of smoking appears to be dose dependant. However, on cessation of smoking the risk increases to higher than that of non smokers [2]. It is assumed that nicotine is the principal constituent in this protective action with its inhibitory effect on the T helper 2 cell function, which are the prime cells involved in UC [5].

Non steroidal anti inflammatory drugs (NSAID) and oral contraceptive pills have also been linked with disease exacerbations. Cornisha *et al.* have shown an association between the use of oral contraceptive pills and IBDs, in particular CD, in their studies [19]. NSAIDs probably act as triggering factors by decreased production of protective mucosal prostanoid and increased leukocyte adherence and migration. Appendectomy in individuals below 20 years for appendicitis or mesenteric lymphadenitis also has a protective effect against UC. This is probably because the inflammatory condition that resulted in appendectomy protected against any future development of UC. Another probable hypothesis is that genetic predisposition to UC might protect against appendicitis [5].

Microbial Factors

Andoh *et al.*, in their studies have shown that the microbial community in the gut of a patient with UC is different from that of healthy individual implicating the possible role of microbial factors in the development of this disease. These organisms included both unclassified bacterial species as well as known bacterial species [20]. Some of the proposed species include *Bacillus* species, adhesive *E. coli*, and *Fusobacterium varium* [2]. In fact, the probable roles of other

organisms like fungi have also been hypothesized [21]. Studies have also led to the conclusion that different bacteria are responsible for inflammatory effect in different individuals [1]. In relation to the hygiene hypothesis, it was observed that infants of the developed world are colonized by the same strain persistently in the gut whereas in the developing world they were colonized by different strains serially [13]. It was also noted that colonization with lactobacilli and bifidobacteria had a protective role to play in the development of IBDs. By reinforcing the immune counter regulatory mechanisms, probiotics and helminth administration was also observed to ameliorate IBDs in both human and experimental models [13]. It was also noted that the recognition of the microbes by certain epithelial cell receptors, Toll like receptors (TLR) and *NOD* proteins play a vital role in the induction of control inflammation and the development of the adaptive immune response, predominantly the Th1 response [13].

Immunology

There is almost universal agreement on the fact that CD is mediated by the T helper 1 cells. On the other hand, though it has been postulated that UC is regulated by the Th2 cells, it is still to be proven. This is based on the increased expression of *IL-5*, a Th2 cytokine. Th2 cells mediate the B cells and antibody response. The increase in IgG plasma cells seen in UC is probably mediated by the Th2 contribution in the antibody response [2]. The importance of toll like receptors (TLR) in the pathogenesis of IBD has been proven by its role in the binding of pathogen associated molecular products (PAMPs) and in the activation of the NF-kappa B pathway. It also plays an important role in the skewing of the naïve T cells towards a Th1 or Th2 profile [22]. It is believed that various environmental factors in genetically predisposed individual trigger the mucosal immune system, specifically the Th2 cells, that release various interleukins like *IL-3*, *IL-4*, *IL-10*, *IL-5* and *IL-13* that result in inflammation of the mucosa and sub mucosa forming crypt abscesses in case of ulcerative colitis [4]. However, there is increasing evidence suggesting the protective role of *IL-10* against IBD [22].

The various theories that have been put forward regarding this immunoregulatory defect are 1) dysfunctional immune host response to normal luminal components 2) Infection with a specific pathogen 3) defective mucosal barrier to luminal antigens. In IBD, the normal downregulation of the inflammatory genes and the normal blocking action of the NF-kappaB pathway by the luminal micro flora is lost resulting in an inflammatory response. This is in contrast to the probable mechanism of the *NOD2* mutations [1].

Free radical and oxidative stress

Pravda in his pioneering studies had proposed the "Radical Induction Theory" to explain the initial entry of WBCs into the colonic mucosa. According to this theory, the excess un-neutralized hydrogen peroxide, produced within colonic epithelial cells diffuses into the extracellular space where it is converted to the highly damaging hydroxyl radical causing oxidative damage to the colonic barrier. This enables the faecal bacterial antigens to invade the normal sterile sub mucosa and provoke the initial immune response [23]. It is also believed that oxidative stress and downregulation of specific detoxification genes may be involved in the pathogenesis of IBD [24]. In fact it was

observed that among the various immunoregulatory factors, reactive oxygen species are present in abnormally high amounts in patients of IBD [25]. Oxidative stress has also been linked with chronic IBD associated colorectal cancer [26].

Pathophysiology

Though the exact cause of ulcerative colitis still remains elusive, a number of findings point towards an overstimulation or inadequate regulation of the mucosal immune system [5]. The characteristic tissue damage and granuloma formation in IBD has been attributed to be the end result of neutrophil migration and degranulation during the initial innate immune response. With respect to the adaptive immune response, it was observed that the cell mediated response was predominantly of a T helper 2 cell types. The naïve T cells were activated in response to the action of the antigen presenting cells like the macrophages and dendritic cells by the secretion of cytokines, which were presumed to be under genetic and environmental influence [1]. In the active stage of the disease, mucosa and sub mucosa become heavily infiltrated with both acute and chronic inflammatory cells. An increase in mucosal IgG production, evidence of complement activation and activation of macrophages and T cells have been observed which results in the release of numerous cytokines, kinins, leukotrienes, platelet activating factors (PAF) and reactive oxygen metabolites. This in turn results in the strengthening of the immune inflammatory response along with their action on the epithelial function, endothelial function, and on the repair mechanisms. Cytokines like IL-1, IL-6 and TNF have been linked with the acute phase response resulting in fever and a rise in serum acute phase proteins [5]. It was observed that an excess of Th2 response was associated with an increased secretion of IL-4, IL-5, IL-10, and IL-13 and they also support a humoral immune response. Another probable hypothesis or co existing factor in the pathogenesis of IBD is a defect in the mature T cells, the Th3 and T regulatory 1, suppressor cells that produce immunoinhibitory cytokines like Transforming growth factor (TGF)-beta and IL-10 [1].

Clinical features and diagnosis

UC runs a protracting course alternating with periods of symptomatic inflammation of shorter duration and disease free intervals which can extend for months, years or even decades [2]. The course of the disease is highly variable as 20 to 50% of patients report spontaneous remission from flare ups whereas 50 to 70% have a relapse during the first year after diagnosis. This relapse rate was found to be higher in younger patients and decreases with advancing age [5]. UC, a relapsing and remitting inflammatory disorder, is limited to the mucosa and sub mucosa of the colon only. However, the small intestine may be involved in cases of “backwash ileitis” [2].

Clinical Features

The patients may come with a myriad of symptoms, the most common being diarrhea with blood and mucus, which may be associated with pain. Fever and weight loss are less frequent. Patients with proctitis commonly complain of obstipation, bloody stools, tenesmus and incontinence of stool. When the disease becomes more extensive and severe, complains of nausea, vomiting and weight loss are more

frequent. Other signs of a long standing disease include malnutrition, weight loss and anemia [2].

The extra intestinal symptoms commonly seen are involvement of the joints (39%) as in arthritis, arthralgia and ankylosing spondylitis. The involvement of the liver and pancreas like fatty liver, hepatitis, primary sclerosing cholangitis and pancreatitis are next in the extra intestinal manifestations. The other involvements seen are iritis, uveitis, conjunctivitis, pyoderma gangrenosum, erythema nodosum and aphthae [5]. Pyoderma gangrenosum and primary sclerosing cholangitis are more commonly seen in ulcerative colitis as compared to Crohn’s disease. Toxic megacolon, perforation and hemorrhage are life threatening complications seen in patients of UC [2,4]. Development of colorectal cancer is another complication seen in patients of UC more so than CD, the risk of which increase with extent of the disease and younger age [2].

Gross and Histological Features

During the active disease, neutrophils can be found infiltrating the mucosa and sub mucosa forming crypt abscesses. A decrease in goblet mucin and shortening of the crypts becoming indistinct and reduce in number has also been reported. The regeneration of these destroyed crypts takes place mostly by Paneth cells. With increase in the severity of the disease, the superficial ulcerations and erosions present can penetrate deeper into the sub mucosa [2]. Ulcerative colitis affects the colon in a continuous manner without any skip lesions. Presence of superficial ulcers and pseudo polyps with an erythematous and friable mucosa is a characteristic feature of UC. These polyps are edematous normal mucosa around the inflamed region. In case of a chronic disease, loss of haustra and mucosal folds with layering of muscularis mucosa is seen. This can lead to hypertrophy of the muscularis mucosa and fibrosis leading to stricture formation [2].

Diagnosis

A diagnosis of Ulcerative colitis can be made only after a number of intestinal inflammatory disorders like infective, vascular, malignant, drug induced and miscellaneous conditions like collagenous colitis or sarcoidosis have been excluded [5].

Treatment

Ulcerative colitis, a disease affecting various aspects of the patient, requires a multidimensional approach. In addition to the control of various intestinal and extra intestinal manifestations, it is also mandatory to provide the patient with nutritional and psychosocial support. Though various advances have been made in the treatment of ulcerative colitis, the quality of life of the patient is greatly compromised with its long remitting and relapsing course and the side effects of these various drugs [4]. There is medical and surgical treatment for the disease depending on its severity and extent. The medical treatment involves a stage of inducing remission and then maintaining this remission with the help of various drugs. The core medical treatment for this condition remains to be corticosteroids, sulfasalazine and its derivatives the 5-amino salicylic acids (5 ASA) and immunosuppressants (6-mercaptopurine, azathioprine, cyclosporine) [5]. In an active unstable disease, anti diarrheal drugs should never be given [4].

The more novel methods of treatment that have emerged, anti-TNF-alpha, anti-alpha four integrin, Peroxisome proliferator-activated receptor gamma (PPAR gamma) ligand and probiotic therapy, are still to prove their clinical efficacy. Transdermal nicotine, short chain fatty acid, fish oil, oral aloe vera, boswellia serrata, bromelain, germinated barley and dietary modifications are some of the other proposed modes of treatment [4]. In UC, colectomy is absolutely indicated only in three conditions: exsanguinating haemorrhage, frank perforation and proven or strongly suspected carcinoma. It is also done in case of severe UC unresponsive to an intensive medical regimen or toxic megacolon [5].

Aminosalicylates

In mild to moderate UC, aminosalicylates with their anti-inflammatory action is the main treatment in both inducing and maintaining remission. It blocks the production of prostaglandins and leukotrienes, inhibits chemotaxis, scavenges oxygen radicals, and inhibits NF-κB. 5-Aminosalicilate (5-ASA), when given in the pure form poses the problem of being completely absorbed in the upper gastrointestinal tract and is thus not available in the colon for its local action. Over the decades, various modes for the delivery of this drug for its local action have developed [4].

Sulfasalazine (Azulfadine) is made up of sulfapyridine and 5-ASA moieties joined by an azo bond. In the colon, the azo bond cleaved by the bacterial flora releases 5-ASA enabling it for its local anti-inflammatory action. Sulfapyridine on the other hand is absorbed by the colon and reaches high serum concentrations [4]. Sulfapyridine with its anti-bacterial action has so far been proved to have no role in the treatment of ulcerative colitis. In fact most of the adverse effects of sulfasalazine have been attributed to this component [4]. These include hypersensitivity reactions or intolerable side effects such as headache, nausea, anorexia and vomiting. Patients are given folic acid supplements as sulfasalazine impairs folic acid absorption. However, it has also been seen that 10% to 20% of individuals, who cannot tolerate sulfasalazine, are intolerant to 5-ASA moiety as well [27]. Sulfasalazine with its low cost and effective action continues to be a mainstay in the treatment of UC, in spite of these intolerable side effects. However in recent decades there has been an outburst of various ingenious methods to deliver 5-ASA moiety without the culpable sulfapyridine moiety [4]. These include alternative azo bonded carriers, 5-ASA dimers, pH dependant tablets, and continuous release preparations. They are as effective as sulfasalazine when used in equimolar concentrations.

Olsalazine (Dipentum) consisting of two 5-ASA moieties and Balsalazide (Colazal) consisting of 5-ASA linked to an inert molecule (4-aminobenzoyl-β-alanine) make use of the same mechanism of cleaving the azo bond by the bacterial flora [4]. However, due to increased secretion into the bowel, 17% of individuals on olsalazine experienced non bloody diarrhoea. The 5-ASA moiety, Mesalamine, has also been incorporated into various enteric coated formulations. Claversal, one such formulation, releases mesalamine at a pH > 6.0, which is present from the mid jejunum to the distal colon. On the other hand, Asacol with its variable disintegration, liberates mesalamine at a pH >7.0. It has a longer gastric dwelling time when taken with a meal and can break up anywhere ranging from the small intestine to the

splenic flexure of the colon. Pentasa, an ethyl cellulose coated mesalamine, enables the drug to diffuse out with the infusion of water into the small beads. Topical enema (Rowasa) and suppository (Canasa) forms of mesalamine have found to be very effective in the treatment of distal UC with minimal side effects [4]. It has been found to be more effective to utilize a combination therapy with an oral and enema form in the treatment of distal and extensive UC. The FDA has given approval for the utilization of a new once daily, high concentration, multi matrix system MMX mesalamine, in the treatment of mild to moderate UC to improve patient adherence [28].

Glucocorticoids

Glucocorticoids are found to be very effective in the induction of remission in patients not responsive to 5-ASA. However, they are not at all useful in the maintenance of remission. Therefore, once remission is achieved they are gradually tapered at a rate of not more than 5 mg/day. It takes several months to discontinue the drug altogether. They can be given in the oral, parenteral or enema form. Even so, topical steroids were found to be not as effective as topical 5-ASA therapy. Moreover, with its rapid absorption from the rectum it causes adrenal suppression and systemic adverse effects on prolonged use. The numerous side effects of steroid therapy include fluid retention, abdominal striae, fat redistribution, hyperglycemia, sub capsular cataracts, osteonecrosis, myopathy, emotional disturbances and withdrawal symptoms. A less toxic form of corticosteroid preparation, budesonide, was found to be useful in distal ileal and right colonic disease but not in transverse and distal colonic disease [4].

Immunosuppressive Medications

6-mercaptopurine (6-MP) and azathioprine (prodrug of 6-MP) are used as glucocorticoid sparing agents to maintain remission in patients not able to wean of glucocorticoids. It takes about 6 months for the drug to start acting during which steroids can be used to induce remission. Once remission is achieved, these drugs take over, enabling steroids to be withdrawn before systemic toxicity ensues. Nausea, fever, rash, hepatitis and bone marrow suppression are the main adverse effects with 3%-4% patients coming with pancreatitis that is reversible on stoppage of the drug. These drugs are either metabolized into 6-methyl mercaptopurine by the enzyme thiopurine methyltransferase (TPMT) or 6-thioguanine by the enzyme hypoxanthine phosphoribosyltransferase. 6-thioguanine is found to be responsible for the immunosuppressive action along with the bone marrow suppression. An 11% population was found to have a heterozygous TPMT with decreased activity leading to the accumulation of the drug and hence toxicity. These adverse effects necessitate strict monitoring during the administration of these drugs [4].

Cyclosporine, a lipophilic peptide, has found to be very effective in the treatment of severe UC. A study showed that approximately 50% to 80% individuals can avoid colectomy on using intravenous cyclosporine [4]. It has been found to have a more rapid onset of action than the above mentioned drugs. However, the oral form of medication has not been found to be very effective on a long term basis as compared to the intravenous form. Therefore, this drug is more suitable to be used as an inducing rather than maintaining agent for remission. It has significant toxicity like

hypertension, gingival hyperplasia, hypertrichosis, paresthesias, tremors, headaches, electrolyte abnormalities. As a result, monitoring is a must during the course of treatment. Tacrolimus and mycophenolate mofetil are other second line immunosuppressive agents available [4]. Tacrolimus was found to be very effective in adults with steroid dependant or refractory UC.

Anti-tumour necrosis factor α treatment

Infliximab, a chimeric mouse clonal human antibody against TNF α , was found to be very effective in the treatment of CD. In the case of UC, however, studies have been rather conflicting. In two large randomized placebo controlled trials, 37% and 49% of patients showed response. In addition 22% and 20% were able to maintain remission. On the contrary, another randomized trial claimed that infliximab had no benefit in steroid resistant UC [29]. Infliximab, 75% human protein and 25% murine protein, was associated with the development of antibodies on administration. Simultaneous treatment with steroid and other immunosuppressive drugs are therefore recommended [4]. Moreover it is also advocated to give periodic infusions rather than episodic or on demand infusions. These practices will reduce the antibody response that results in decreased response to treatment. Adverse effects include serum sickness, acute infusion reactions, increased risk of infections and rarely lymphomas. To reduce the immunogenicity newer drugs like CDP571 (95% human protein 5% murine protein) and etanercept (100% human protein) were introduced, but these drugs were found to be less effective than infliximab [4]. Studies pertaining to Adalimumab, a fully human IgG1 monoclonal antibody that is administered subcutaneously, in the treatment of UC are going on [30].

Potential treatment options

Various advances have emerged in the treatment of UC with better understanding of the pathogenesis of the disease in recent years. This might usher a new era in the management of the disease with significant improvement in the quality of life of patients. Natalizumab, a recombinant IgG4 humanised monoclonal antibody against $\alpha 4$ integrins, was found to be effective in increasing the number of clinical remissions with just two doses given 4 weeks apart. $\alpha 4$ integrins are involved in the recruitment of human leukocytes [4]. MLN-02, a monoclonal antibody specifically against $\alpha 4\beta 7$, was found to be very effective in inducing remission and was generally well tolerated. However, more studies are required regarding the same [30]. Another study showed that PPAR γ (peroxisome proliferator-activated receptor γ) ligand, rosiglitazone maleate, was useful to patients with active UC. There has been found to be a reduced expression of these receptors in the diseased colon. PPAR γ gene therapy can also be effective to improve the endogenous anti-inflammatory activity [4]. Monoclonal antibodies that hold the potential to be a breakthrough in the treatment of ulcerative colitis include anti- $\alpha 4\beta 7$ [vedolizumab]), anti-cell adhesion molecule inhibitors (abatacept) and newer anti-cytokine therapies (anti-IL-17). Though anti-IL-12 has not been met with success in follow-up clinical trials, but MLN02 still holds promise for maintenance of remission. Among these newer monoclonal antibodies, clinical trials have shown a positive future for vedolizumab in active UC [31].

Anti CD4 antibodies were found to be effective in achieving remission in UC patients in 3 separate trials. However, due to the risks associated with CD4 lymphopenia further studies in this regard have ceased. Anti CD10 antibodies were also found to be effective in a phase 1 study conducted but the results were obtained from a very small number of individuals making the study inconclusive. Even though phase 2 placebo controlled trial failed to show any efficacy in the use of anti-inflammatory cytokine IL-10, with the use of genetically engineered lactobacillus for the delivery of the drug, it might hold a promising alternative. Basiliximab, a monoclonal anti CD25 antibody was found to be effective as a steroid sensitizing agent in steroid resistant patients. Daclizumab, a monoclonal antibody targeting CD25, was found to be successful in achieving remission in patients with active ulcerative colitis in a clinical trial [32]. Alcaforfen (ISIS 2302) enema that causes a reduction in ICAM protein 1 expression was found to be very effective in the treatment of distal UC in a randomised placebo controlled trial. Epidermal growth factors, though found effective in UC, raise the dilemma of probable malignant transformation in susceptible individuals [30]. Theoretically growth factors like epidermal growth factor, keratinocyte growth factors, growth hormone, teduglutide, and GM-CSF/G-CSF are potential tools in the treatment of ulcerative colitis. However, clinically epidermal growth factor and keratinocyte growth factor 2 did not live up to the expectation [32].

With the unearthing of various mechanisms involved in the evolution of the disease, attention has been diverted to the inhibition of various cytokines involved in the activation of TH cell pathway. One such approach is to block this pathway by using agents that inhibit NF- $\kappa\beta$ [1]. Other therapeutic targets include modulators of CD80 or CD86-CD28 co-stimulatory signal (abatacept), CD2 receptors on T-cells (alefacept), CD11a, subunit of leukocyte function-associated antigen 1 (efalizumab), vitronectin receptor, and CD20 antigen on pre-B, immature, and mature B cells (rituximab) [32]. Another novel method being explored is apheresis, removal of leukocytes from the peripheral blood, with an aim to reduce the inflammatory response [1]. In fact, Granulocyte and Monocyte apheresis have shown positive results when used in retreatment of patients with chronically active inflammatory bowel disease [33].

In spite of conflicting results, many physicians have used antibiotics (Rifaximin, Tobramycin, Amoxicillin, metronidazole) in conjunction with standardised treatments for ulcerative colitis. This arena is still to be explored further for its potential in treatment [32]. Transdermal nicotine, short chain fatty acids like fish oil, probiotics (Nissle 1917, VSL-3), unfractionated or low molecular weight heparin, anti-oxidants and plant products (euphol) are other treatment regimens which are found to be effective in the management of UC [4,32,34]. Studies have shown that probiotics like VSL#3 were more superior than placebos when used in combination with standard conventional treatments of ulcerative colitis [35,36]. Rectally administered probiotic, *Escherichia coli* Nissle 1917 (EcN), was found to have a significant effect on the disease activity index of acute distal ulcerative colitis [37]. In solidarity with the hygiene hypothesis, clinical trials have shown that helminths specifically *Trichuris suis*, are effective in the prevention and treatment of ulcerative colitis [32]. In addition, Cholera B subtoxin was found to ameliorate experimentally induced colitis in mice [32].

Conclusion

Ulcerative Colitis, a disease of the developed world, is emerging as one of the many banes of development in India. It is sure to create a huge hole in our rapidly growing economy with a substantial decline in the quality of life of individuals. Though the exact etiology and pathogenesis of ulcerative colitis still remains elusive, recent years have seen a tremendous improvement in the treatment options

available to patients. Further clinical trials have to be conducted regarding the new and potential treatment options available with the better understanding of the etiopathology day by day. This knowledge in the future might even lead to the start of a preventive phase in the management of ulcerative colitis.

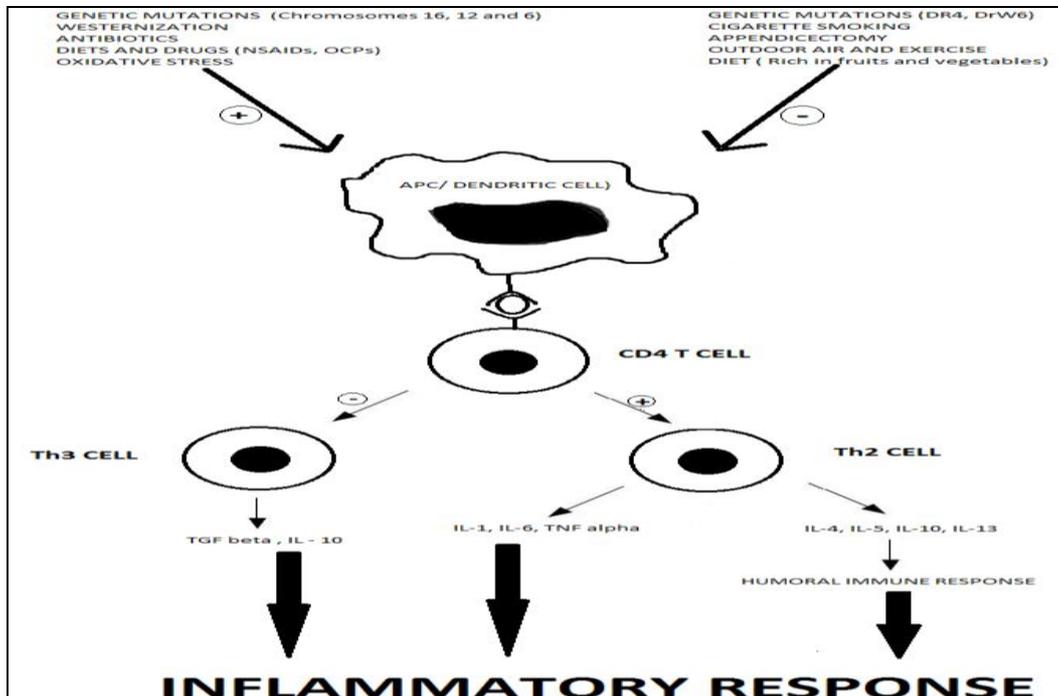


Fig 1: Schematic representation of the probable pathogenesis of Ulcerative colitis

Table 1: Treatment options of ulcerative colitis

Aminosalicylates	Sulfasalazine
	Olzastatine
	Balsalazide
	Melsalamine enteric coated formulations
Topical enema and suppository forms	
Glucocorticoids	Oral
	Parenteral
	Enema
Immunosuppressive	6 Mercaptopurine
	Azathioprine
	Cyclosporine
	Tacrolimus
	Mycophenolate mofetil
Anti Tumour Necrosis Alpha	Infliximab
	CDP 571
	Etanercept
	Adalimumab
Potential Treatment	Natalizumab
	Rosiglitazone maleate
	Vedolizumab
	Abatacept
	Anti IL-17
	MLN02
	Anti CD 4 and anti CD 10 antibodies
	Basiliximab
	Daclizumab
	Alcaforsen
Growth factors, probiotics, antibiotics	

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