ORIGINAL RESEARCH PAPER
Volume - 11 | Issue - 02 | February - 2022 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ULCERATIVE COLITIS –A REVIEW

General Medicine

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ABSTRACT

Ulcerative colitis is an inflammatory bowel disease. It causes inflammation and sores, called ulcers, in the lining of the rectum and colon. Ulcerative proctitis is endoscopically characterized by edema, erythema and loss of vascular markings. Ulcerative colitis has been reported between 1.0 and 15.0 cases per 100,000. The pathogenesis of ulcerative colitis remains unknown. Several theories have been proposed that implicate vascular impairment, autoimmune mechanisms, bacterial-immunological interactions, and allergic or hypersensitivity reactions. Ulcerative colitis is one of the major two types of inflammatory bowel disease (IBD), along with crohn's disease (CD). The differential diagnosis in ulcerative colitis includes other forms of inflammatory bowel disease, including Crohn's disease, diverticular inflammation and hemorrhage, collagenous colitis, ischemic bowel disease, radiation colitis, and infectious etiologies including the following organisms: Campylobacter, Shigella, Clostridium difficile, amebiasis, and Escherichia coli 0157:H7.

Conventional drug therapy for UC involves use of aminosalicylates, corticosteroids, azathioprine/6-mercaptopurine, cyclosporine and anti-tumor necrosis factor therapy. Alternative therapies include probiotics, nicotine and fish oil. Drugs like tacrolimus, rosiglitazone and Trichuris suis ova are being evaluated for use in UC patients. Anti-inflammatory drugs (adrenocorticosteroids and compounds containing 5-aminosalicylic acid) are the mainstays of medical therapy.

These medications in a variety of forms are used orally and topically to reduce inflammation of the colon and rectum. Surgery in ulcerative colitis should be reserved for those patients with refractory disease, complications associated with the medical therapy, or complications of colitis.

KEYWORDS

Ulcerative colitis, crohn's disease.

AIM AND OBJECTIVE

In this article, we will discuss symptoms ,signs,pathophysiology ,investigations, medical therapies and management strategies of Ulcerative Colitis. according to the severity and extent of UC.

INTRODUCTION

Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disorder of the colon that causes continuous mucosal inflammation extending from the rectum to the more proximal colon, with variable extents. UC is characterized by a relapsing and remitting course. UC was first described by Samuel Wilks in 1859 and it is more common than Crohn's disease worldwide. The overall incidence and prevalence of UC is reported to be 1.2–20.3 and 7.6–245 cases per 100,000 persons/year respectively. UC has a bimodal age distribution with an incidence peak in the 2nd or 3rd decades and followed by second peak between 50 and 80 years of age. The key risk factors for UC include genetics, environmental factors, autoimmunity and gut microbiota. The classic presentation of UC include bloody diarrhea with or without mucus, rectal urgency, tenesmus, and variable degrees of abdominal pain that is often relieved by defecation. UC is diagnosed based on the combination of clinical presentation, endoscopic findings, histology, and the absence of alternative diagnoses. In addition to confirming the diagnosis of UC, it is also important to define the extent and severity of inflammation, which aids in the selection of appropriate treatment and for predicting the patient's prognosis Ileocolonoscopy with biopsy is the only way to make a definitive diagnosis of UC.Abdominal computed tomographic (CT) scanning is the preferred initial radiographic imaging study in UC patients with acute abdominal symptoms. The Mayo scoring system is a commonly used index to assess disease severity and monitor patients during therapy. The goals of treatment in UC are three fold—improve quality of life, achieve steroid free remission and minimize the risk of cancer. The choice of treatment depends on disease extent, severity and the course of the disease. For proctitis, topical 5-aminosalicylic acid (5-ASA) drugs are used as the first line agents. UC patients with more extensive or severe disease should be treated with a combination of oral and topical 5-ASA drugs +/− corticosteroids to induce remission. Patients with severe UC need to be hospitalized for treatment. The options in these patients include intravenous steroids and if refractory, calcineurin inhibitors (cyclosporine, tacrolimus) or tumor necrosis factor-α antibodies (infliximab) are utilized. Once remission is induced, patients are then continued on appropriate medications to maintain remission. Indications for emergency surgery include refractory toxic megacolon, colonic perforation, or severe colorectal bleeding.

Pathophysiology

The pathogenic mechanism of UC is still not completely clear. Modern medicine considers the development of UC to be associated with a variety of factors, mainly including environmental factors, immune factors, inflammation, eating disorders, emotional distress, and genetics.

A pathognomonic finding of UC is the presence of continuous colonic inflammation characterized by erythema, loss of normal vascular pattern, granularity, erosions, friability, bleeding, and ulcerations, with distinct demarcation between inflamed and non-inflamed bowel. Histopathology is the definitive tool in diagnosing UC, assessing the disease severity and identifying intraepithelial neoplasia (dysplasia) or cancer. The classical histological changes in UC include decreased crypt density, crypt architectural distortion, irregular mucosal surface and heavy diffuse transmucosal inflammation, in the absence of genuine granulomas.

Signs And Symptoms

The most common presenting symptoms of UC are diarrhea and blood in the stool. Additionally, depending on the severity and location of the disease, patients may also report varying degrees of abdominal pain, nocturnal diarrhea, mucus discharge, urgency, and/or tenesmus. In rare cases with severe inflammation and especially in those with prolonged untreated UC before diagnosis, patients may present with weight loss, fevers, or perforation.

Symptoms typically start gradually and evolve over several weeks. In as many as 25% of patients, extraintestinal manifestations (EIMs) may predate the onset of gastrointestinal symptoms.

Severity and Location of Disease Ulcerative colitis is categorized according to the Truelove and Witts criteria as mild, moderate, severe, or fulminant .

Mild disease-- Patients with less than 4 bowel movements per day (with or without blood) with normal inflammatory markers and without systemic toxicity are categorized as having mild disease. Patients with mild disease usually present with intermittent rectal bleeding associated with the passage of mucus, and mild diarrhea with fewer than four small loose stools per day. Mild crampy pain, tenesmus, and periods of constipation are also common.

Severe abdominal pain, profuse bleeding, fever, and weight loss are not the symptoms. and signs of mild disease.

Moderate disease – is characterized by frequent loose, bloody stools (up to 10 per day), mild anemia not requiring blood transfusions, abdominal pain that is not severe, and low grade fever.

Severe disease -- These patients present with frequent loose stools (>10 per day), severe cramps, high-grade fever and bleeding often requiring blood transfusion. They may also have rapid weight loss.

Fulminant disease-- Patients with fulminant disease are defined as having more than 10 bloody bowel movements per day and clinical signs of toxicity such as abdominal distention, blood transfusion requirements, and colonic dilation noted on radiography. Up to 15% of patients will initially present with severe disease.34

TABLE 1. Truelove and Witts Criteria for Ulcerative Colitis

Variable	Mild	Severe	Fulminant
Bowel movements per day	<4	>6	>10
Bloody stool	Intermittent	Frequent	Continuous
Temperature	Normal	>37.5°C	>37.5°C
Heart rate	Normal	>90 beats/min	>90 beats/min
Hemoglobin	Normal	<10.5 g/dL	Requiring transfusion
Erythrocyte sedimentation rate	≤30 mm/h	>30 mm/h	>30 mm/h
Colonic findings on imaging	Normal	Edematous wall, thumbprinting	Dilation
Clinical signs	Normal	Abdominal tenderness	Abdominal distention and tenderness

UC is also sub classified on the basis of the extent of the disease: Proctitis -----limited to the rectum; Distal colitis or proctosigmoiditis ----refers to disease extending to the mid-sigmoid colon, usually reachable by a 60 cm flexible sigmoidoscope.; Left-sided colitis ----- refers to disease extending to but not beyond the splenic flexure Extensive colitis------. Extensive colitis is defined as disease that extends beyond the splenic flexure but not as far as the cecum. Pancolitis ----is used when the inflammatory process extends to the cecum Extraintestinal Manifestations of UC There are many EIMs associated with UC, but they most commonly affect the skin, joints, eyes, and liver. Arthropathies are the most common EIM. Erythema nodosum and pyoderma gangrenosum(PG) are the 2 most common immunologic skin lesions in UC. Primary sclerosing cholangitis (PSC) has an estimated prevalence of approximately 5% in UC. Primary sclerosing cholangitis is more common in males and often diagnosed between ages 30 and 40 years. It can be a progressive disease resulting in cirrhosis. PSC is a risk factor for development of cholangio carcinoma and colon cancer.

Diagnosis

Ulcerative colitis is diagnosed on the basis of presenting symptoms consistent with the disease and findings on sigmoidoscopy or colonoscopy showing continuous colonic inflammation starting in the rectum . Biopsies of the colon are confirmatory when specimens showing findings consistent with chronic inflammatory changes.

The biopsy shows that disease remains limited to the mucosal layers (ie, not transmural) with Paneth cell metaplasia, mucin depletion, distortion of crypt architecture, crypt abscesses, and infiltrates of the mucosa with lymphocytes, plasma cells, and granulocytes.

Laboratory tests

Blood tests -- should include routine testing (eg, complete blood cell count, Comprehensive metabolic panel, ferritin, vitamin D) as well as inflammatory markers(eg, C-reactive protein and sedimentation rate).
Stool examination-- should be sampled to exclude Clostridium difficile, Escherichia coli, Salmonella, and Shigella. Additionally, stool can also be tested for fecal calprotectin, a protein found in polymorphonuclear leukocytes that if low has high negative predictive value for IBD, with only a 1% chance of IBD in such cases.

Ileocolonoscopy with biopsy is the only way to make a definitive diagnosis of UC.

CT--Abdominal computed tomographic (CT) scanning is the preferred initial radiographic imaging study in UC patients with acute abdominal symptoms. The hallmark CT finding of UC is mural thickening with a mean wall thickness of 8 mm, as opposed to a 2–3 mm mean wall thickness of the normal colon.

Management

The goal of therapy in UC is to first induce a clinical remission and then attain steroid free maintenance of remission.

Mild to moderate disease is treated with 5- ASA (5-amino salysilic acid). Most treatments involve the use of oral mesalamine. Mesalamine is effective in both inducing and maintaining remission. Doses of 2 g or higher are more effective than low dose mesalamine (<2 g).

In patients with proctitis, proctosigmoiditis, or any disease extent with severe rectal symptoms (eg, urgency and tenesmus), the addition of rectal therapy with mesalamine suppositories or enemas is recommended.

When the disease is mild to moderate and limited to the left side of the colon, topical therapy with enemas and/or suppositories is very effective in inducing and maintaining remission.In general, combining oral and rectal 5-ASA is most effective.Response to therapy is typically seen within 14 days of initiation but can take up to 8 weeks to induce remission. Once remission is achieved, patients usually continue the drug for maintenance therapy. Overall, mesalamine is a safe and effective medication. Typical adverse effects of mesalamine include headache , nausea, paradoxical reactions resulting in worsening diarrhea as well as a 0.2% risk of drug induced interstitial nephritis . Sulfasalazine : causes hemolytic anemia, leukopenia hepatitis. Routine monitoring of kidney function is recommended to screen for interstitial nephritis.

In cases in which the disease is still not controlled and with more prominent rectal symptoms, either rectal corticosteroid enemas or foam are added to the initial regimen. In cases of more extensive colitis but only mild to moderate flares of disease, an oral colonicrelease formulation of budesonide (budesonide MMX) can be used.

Moderate to Severe Disease

The initial management of moderate to severe disease is typically with systemic corticosteroids using oral prednisone or in more severe cases, intravenous (IV) corticosteroids. In addition to corticosteroids, a corticosteroid sparing agent should be added to the medication regimen for long-term corticosteroid-free maintenance of remission.

The choice of which drug to add depends on disease severity. Corticosteroids should never be used as long-term therapy and are only utilized to induce remission.

For maintenance of remission, there are a number of different therapeutic classes including thiopurines, anti-TNF, anti-integrins, and a Janus kinase inhibitor. Aside from the thiopurines, which are only effective in maintenance of remission, the other drug classes all have efficacy in inducing and maintaining remission. Typically, only one immunosuppressant or biologic agent is used, but some data suggest that combining an anti-TNF with an immunosuppressant is more effective than either agent alone.

Corticosteroids. Corticosteroids are only used for the induction of remission. They have no role in long-term disease maintenance. oral prednisone is the preferred corticosteroid and initiated at a dose of between 40 and 60 mg/d.

The patients with severe-fulminant colitis require hospitalization for close monitoring of disease severity and the risk of disease complications. Two-thirds of patients will respond to IV corticosteroids at doses of 40 to 60 mg/d of methylprednisolone regardless of previous corticosteroid exposure. If the UC fails to respond to IV corticosteroids,then rescue therapy with infliximab or cyclosporine or surgical treatment should be kept in mind.

Although corticosteroids are very effective at inducing remission, they are associated with a number of complications, many of which are often irreversible.The complications are Osteopenia, Osteoporosis, Avascular necrosis, Adrenal insufficiency, Infection, Weight gain

,Insomnia ,Mood changes ,Delirium, Cataracts, Glaucoma, Skin changes and Delayed wound healing.

Thiopurines. Thiopurines (eg, azathioprine and mercaptopurine) are utilized to maintain remission but have no role in the induction of remission. The drugs have very slow onset of action, with pharmacological steady state reached within 2 to 3 weeks but typically taking up to 12 weeks to achieve a therapeutic effect. Both leukopenia and elevated liver function test results are typically related to the activity of the thiopurine methyltransferase (TPMT) enzymes. Current guidelines recommend testing for TPMT enzymatic activity before initiating thiopurine. If the enzymatic activity is low or not present, as seen in 0.3% of the population, then this class of drugs should not be used. The typical starting dose of mercaptopurine is 1 to 1.5 mg/kg and for azathioprine, 2 to 2.5 mg/kg body wt.

The side effects of thiopurins are Nausea,vomiting, Hepatitis, Leukopenia, Pancreatitis ,Infection, Non-Hodgkin lymphoma, Nonmelanoma skin cancer and Cervical dysplasia.

Anti-TNF Agents. Anti-TNF agents can be used for both induction and maintenance of remission. In most cases, similar to thiopurines, they are used in conjunctionwith corticosteroids to induce remission. However, in selected moderately severe cases, one may consider using anti-TNF therapy without corticosteroids to induce remission. At this time, there are 3 anti-TNF agents approved for use in moderate to severe UC: infliximab, adalimumab, and golimumab. All but infliximab are fully human antibodies and are self-injectable. Infliximab is a chimeric anti- TNF antibody (75% human, 25% murine) that is administered IV Infliximab may be slightly superior to adalimumab and golimumab, with higher rates of induction of remission and mucosal healing.Before giving this drug the Latent tuberculosis and Hepatitis B must be ruled out in the patient. The most common adverse effect is risk of infections. Most of these infections are nonserious (eg, common cold, otitis media, sinusitis). Other risks include abnormalities on laboratory testing and elevated liver function test results as well as a small risk of both melanoma and lymphoma.

Response to anti-TNF therapymay be seen as early as 3 days after the first dose but can take as long as 6 to 12 weeks to achieve initial response and mucosal healing. Additionally, all these drugs carry a risk of antibody development. In some situations, to reduce the risk of antibody formation while the patient is receiving anti-TNF therapy, clinicians may opt to combine anti-TNF therapy with a thiopurineor methotrexate.

Calcineurin Inhibitors. In cases of severe refractory UC unresponsive to IV corticosteroids, cyclosporine can be considered as an alternative to infliximab for rescue therapy, with one study reporting equal effectiveness to infliximab in this setting. Intravenous cyclosporine can be used in this situation with response seen within 48 hours. However, it is not a long-term solution because the oral formulation is not an effective maintenance option. If a patient responds to IV cyclosporine, they are typically transitioned to oral cyclosporine with a long-term maintenance plan of either a thiopurine or an anti-integrin.

Anti-integrins. Vedolizumab was the first anti-integrin approved for use in moderate to severe UC. It is a selective adhesion molecule that is a fully human monoclonal antibody that blocks the adhesion molecule a4b7-heterodimer. This results in a blockade of leukocyte migration and subsequent gut inflammation. Although the drug has efficacy in inducing remission, it is most effective in maintaining remission in moderate to severe UC. Vedolizumab is a fully human antibody that is IV dosed. Although the drug may produce some initial response within 6 weeks, the main effect of the drug is typically seen 4 to 6 months after starting therapy.

Overall, vedolizumab is considered to be the safest available biologic to treat UC. The main adverse effect is enteric infections. There is a theoretical risk of development of progressive multifocal leukoencephalopathy, a viral brain infection resulting in severe disability and death. In the initial studies and postmarketing surveillance, there have been no cases of progressive multifocal leukoencephalopathy reported with vedolizumab.

Janus Kinsase Inhibitor. Tofacitinib is the newest drug for moderate to severe UC (approved in 2018).It is an oral smallmolecule Janus kinase inhibitor that is effective in both anti-TNFenaive patients and in those with prior anti-TNF exposure.

A recent network meta-analysis indicated that tofacitinb had the highest rank for induction of clinical remission (OR, 11.88; 95% CI, 2.232-60.89).Initial drug efficacy can be seen within 6 weeks.

Tofacitinib is associated with adverse effects similar to those of anti-TNF agents. The most common are infections and specifically reactivation of herpes zoster. To help mitigate this risk, many advise vaccinations with the inactivated zoster vaccine before initiating therapy with tofacitinib. It is unknown if the drug can be used as a rescue therapy in patients whose UC is unresponsive to IV corticosteroids like infliximab and cyclosporine.

Surgery. Despite available medical treatments, approximately 15% of patients require surgery for their disease.The most common indications for surgery include toxic megacolon, perforation, uncontrollable hemorrhage, failing medical therapy (or corticosteroid dependence), cancer, or unresectable dysplasia. In patients younger than 70 years, the typical surgical treatment is a total proctocolectomy with end-ileostomy or ileal poucheanal anastomosis.Most patients prefer the ileal poucheanal anastomosis because it maintains the flow of stool through the anus and avoids a permanent ostomy. This procedure can be performed in 2 or 3 stages. Typically, the colon is removed and a short segment of rectum left in place with a temporary diverting ileostomy. A second stage is then performed in which the Jpouch is formed and connected to the rectum, and the third and final surgical procedure is taking down the ileostomy.

In general, the surgery iswell tolerated, but mild complications are common. After surgery, patients will have 4 to 8 bowel movements during the day and up to 1 to 2 bowel movements overnight. Use of loperamide and/or fiber wafers can reduce the frequency of the bowel movements. Following surgery, nearly 50%of patients will experience episode(s) of pouchitis, which is inflammation of the J-pouch. This complication can result in chronic pouchitis in up to 15% of patients. In most cases, pouchitis is easily treated with antibiotics and/or probiotics.

Pouchitis The most frequently observed long-term complication of ileal pouch anal anastomosis (IPAA) is acute and/or chronic inflammation of the ileal reservoir, called pouchitis. Antibiotics such as metronidazole can be used to treat pouchitis [Sandborn, 1994]. Oral metronidazole 1–2 g/day for 7 days can be given. One double-blind crossover trial randomly assigned patients with chronic unremitting pouchitis to metronidazole (400mg three times daily for 7 days) or placebo [Madden et al. 1994]. Metronidazole was associated with a significant reduction in stool frequency by three movements per day (versus an increase of one per day with placebo) but there was not change in the endoscopic or histologic grade of inflammation. Patients resistant to metronidazole can be treated with other antibacterial agents such as ciprofloxacin, doxycycline or ampicillin. The probiotic VSL#3 has been shown to be effective for primary and secondary prevention of pouchitis Most patients report a dramatic improvement in overall quality of life following surgery.

CONCLUSION

Ulcerative colitis is a chronic inflammatory condition that in most cases requires medication to induce and maintain a long-term corticosteroid- free remission. However, up to 15% of patients may require colectomy to treat their disease. Both UC alone and the medications used to treat UC increase the risks of complications, many of which are potentially preventable.

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